

SUBSTITUTED AMINO CARBOXAMIDES FOR
THE TREATMENT OF ALZHEIMER'S DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Serial Number 60/345,316, filed January 4, 2002, and U.S. Provisional Application Serial Number 60/350,419, filed January 18, 2002, the disclosure of each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

10 Field of the Invention

The invention relates to substituted amino carboxamides and to such compounds that are useful in the treatment of Alzheimer's disease and related diseases. More specifically, it relates to such compounds that are capable of inhibiting 15 beta-secretase, an enzyme that cleaves amyloid precursor protein to produce amyloid beta peptide (A beta), a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

Background of the Invention

20 Alzheimer's disease (AD) is a progressive degenerative disease of the brain primarily associated with aging. Clinical presentation of AD is characterized by loss of memory, cognition, reasoning, judgment, and orientation. As the disease progresses, motor, sensory, and linguistic abilities 25 are also affected until there is global impairment of multiple cognitive functions. These cognitive losses occur gradually, but typically lead to severe impairment and eventual death in the range of four to twelve years.

Alzheimer's disease is characterized by two major 30 pathologic observations in the brain: neurofibrillary tangles and beta amyloid (or neuritic) plaques, comprised predominantly of an aggregate of a peptide fragment known as A beta. Individuals with AD exhibit characteristic beta-amyloid deposits in the brain (beta amyloid plaques) and in cerebral 35 blood vessels (beta amyloid angiopathy) as well as

neurofibrillary tangles. Neurofibrillary tangles occur not only in Alzheimer's disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for
5 memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of
10 individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition
15 of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor
20 protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A
30 description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase
35 cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin.

See, for example, Sinha et al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a 5 seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD 10 patients has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. 15 In vivo processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

BACE1 knockout mice fail to produce A beta, and present a 20 normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase 25 activity and reduction of A beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's 30 disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

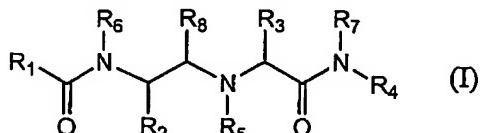
Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are 35 effective inhibitors of A beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the

treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

SUMMARY OF THE INVENTION

The invention encompasses the compounds of formula (I) shown below, pharmaceutical compositions containing the compounds and methods employing such compounds or compositions in the treatment of Alzheimer's disease and more specifically compounds that are capable of inhibiting beta-secretase, an enzyme that cleaves amyloid precursor protein to produce A-beta peptide, a major component of the amyloid plaques found in the brains of Alzheimer's sufferers.

In one aspect, the invention provides compounds of the formula I:



and pharmaceutically acceptable salts thereof, wherein
R₁ is H, R'₁₀₀, -(CRR')₁₋₆R'₁₀₀, -(CRR')₁₋₆-O-R'₁₀₀, -(CRR')₁₋₆-S-
R'₁₀₀, -(CRR')₁₋₆-C(=O)-R'₁₀₀, -(CRR')₁₋₆-SO₂-R'₁₀₀ or -
20 (CRR')₁₋₆-NR₁₀₀-R'₁₀₀;

R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀ alkylaryl or C₁-C₁₀ alkylheteroaryl;

R₁₀₀ and R'₁₀₀ independently represent aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W- heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-

$(CH_2)_{0-4}-CONR_{102}R_{102}'$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(CH_2)_{0-4}(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-R_{110}$, $-(CH_2)_{0-4}-R_{120}$, $-(CH_2)_{0-4}-R_{130}$, $-(CH_2)_{0-4}-CO-R_{110}$, $-(CH_2)_{0-4}-CO-R_{120}$, $-(CH_2)_{0-4}-CO-R_{130}$, $-(CH_2)_{0-4}-CO-R_{140}$, $-(CH_2)_{0-4}-CO-$
5 $O-R_{150}$, $-(CH_2)_{0-4}-SO_2-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(CH_2)_{0-4}(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(R_{150})-CO-O-R_{150}$, $-(CH_2)_{0-4}-N(R_{150})-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-N(R_{150})-CO-R_{105}$, $-(CH_2)_{0-4}-NR_{105}R'_{105}$, $-(CH_2)_{0-4}-R_{140}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-(O-R_{110})_2$, $-(CH_2)_{0-4}-O-CO-N(R_{150})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{150})_2$, $-(CH_2)_{0-4}-O-(R_{150})$, $-(CH_2)_{0-4}-O-R_{150}'-COOH$, $-(CH_2)_{0-4}-S-(R_{150})$, $-(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, $-(CH_2)_{0-4}-C_3-C_7$
10 cycloalkyl, (C_2-C_{10}) alkenyl, and (C_2-C_{10}) alkynyl, or
15 R_{100} is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 R_{115} groups, or
 R_{100} is $-(C_1-C_6$ alkyl)-O-(C_1-C_6 alkyl) or $-(C_1-C_6$ alkyl)-S-(C_1-C_6 alkyl), each of which is optionally substituted with 1, 2,
20 or 3 R_{115} groups, or
 R_{100} is $-O-(CH_2)_{n_8}-R_{4-5}$ where n_8 is 0 thru 2 and R_{4-5} is C_1-C_6 alkyl or aryl, or
 R_{100} is C_3-C_8 cycloalkyl optionally substituted with 1, 2, or 3
25 R_{115} groups;
 W is $-(CH_2)_{0-4}-$, $-O-$, $-S(O)_{0-2}-$, $-N(R_{135})-$, $-CR(OH)-$ or $-C(O)-$;
 R_{102} and R_{102}' independently are hydrogen, or
 C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups
30 that are independently halogen, aryl or $-R_{110}$;
 R_{105} and R'_{105} independently represent $-H$, $-R_{110}$, $-R_{120}$, C_3-C_7 cycloalkyl, $-(C_1-C_2$ alkyl)-(C_3-C_7 cycloalkyl), $-(C_1-C_6$ alkyl)-O-(C_1-C_3 alkyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkyl chain with one double bond and one triple bond, or
35 C_1-C_6 alkyl optionally substituted with $-OH$ or $-NH_2$; or, C_1-C_6 alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, or

R_{105} and R'_{105} together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring, where one member is optionally a heteroatom selected from $-O-$, $-S(O)_{0-2}-$, $-N(R_{135})-$, the ring being optionally substituted with 1, 2 or 3 independently selected R_{140} groups;

5 R_{115} at each occurrence is independently halogen, $-OH$, $-CO_2R_{102}$, $-C_1-C_6$ thioalkoxy, $-CO_2$ -phenyl, $-NR_{105}R'_{135}$, $-SO_2-(C_1-C_8$ alkyl), $-C(=O)R_{180}$, R_{180} , $-CONR_{105}R'_{105}$, $-SO_2NR_{105}R'_{105}$, $-NH-CO-(C_1-C_6$ alkyl), $-NH-C(=O)-OH$, $-NH-C(=O)-OR$, $-NH-C(=O)-O-phenyl$, $-O-C(=O)-(C_1-C_6$ alkyl), $-O-C(=O)$ -amino, $-O-C(=O)$ -mono- or dialkylamino, $-O-C(=O)$ -phenyl, $-O-(C_1-C_6$ alkyl)- CO_2H , $-NH-SO_2-(C_1-C_6$ alkyl), C_1-C_6 alkoxy or C_1-C_6 haloalkoxy;

10 R_{135} is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, $-(CH_2)_{0-2-}(aryl)$, $-(CH_2)_{0-2-}(heteroaryl)$, or $-(CH_2)_{0-2-}(heterocyclyl)$;

15 R_{140} is heterocyclyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, amino(C_1-C_6)alkyl, mono(C_1-C_6)alkylamino(C_1-C_6)alkyl, di(C_1-C_6)alkylamino(C_1-C_6)alkyl, and $=O$;

20 R_{150} is hydrogen, C_3-C_7 cycloalkyl, $-(C_1-C_2$ alkyl)-(C_3-C_7 cycloalkyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl with one double bond and one triple bond, $-R_{110}$, $-R_{120}$, or C_1-C_6 alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from $-OH$, $-NH_2$, C_1-C_3 alkoxy, R_{110} , and halogen;

25 R_{150}' is C_3-C_7 cycloalkyl, $-(C_1-C_3$ alkyl)-(C_3-C_7 cycloalkyl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkyl with one double bond and one triple bond, $-R_{110}$, $-R_{120}$, or C_1-C_6 alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from $-OH$, $-NH_2$, C_1-C_3 alkoxy, R_{110} , and halogen;

30 R_{180} is selected from morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl,

homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl, each of which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C₁-C₆ alkyl, C₁-C₆ alkoxy,

5 halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, and =O;

10 R₁₁₀ is aryl optionally substituted with 1 or 2 R₁₂₅ groups;

R₁₂₅ at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or

15 C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

20 C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;

R₁₂₀ is heteroaryl; which is optionally substituted with 1 or 2 R₁₂₅ groups; and

25 R₁₃₀ is heterocyclyl optionally substituted with 1 or 2 R₁₂₅ groups;

R₂ is

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-

30 N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently

selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or - (CH₂)₀₋₃₋(C₃-C₈) cycloalkyl wherein the cycloalkyl is 5 optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂- (C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N- (C₁-C₆ alkyl) (C₁-C₆ alkyl), or 10 aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted 15 with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R', -C(=O)- (C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino, -SO₂- (C₁-C₄) alkyl, C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 20 groups which are independently selected from halogen, C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, 25 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and 30 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo; 35 R₃ is H or is

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or 5 - (CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or 10 aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from 15 halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄) alkyl, 20 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, -C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, -C₁-C₆ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, 25 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, 30 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and 35

5 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is
optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, -SH,
-C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and
mono- or dialkylamino; and the heterocyclyl
group is optionally further substituted with
oxo;

R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -
(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-

10 heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-heterocyclyl,
-(CR₂₄₅R₂₅₀)₀₋₄-aryl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-aryl,
-(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-
heteroaryl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heterocyclyl, -
heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heterocyclyl, -

15 (CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-aryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-
(R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂,
-CH(heterocyclyl)₂, -CH(aryl)(heteroaryl), -(CH₂)₀₋₁-
CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl, -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-
(CH₂)₀₋₁-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C₁-
20 C₄ alkyl), -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂, (C₁-C₆
alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂,
-(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀), or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
independently selected from the group consisting of

25 R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH,
-NR₂₃₅C=ONR₂₃₅R₂₄₀, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀, or
-(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is

optionally substituted with 1, 2, or 3 groups

independently selected from the group consisting of

30 R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆
alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or

cyclopentyl, cyclohexyl, or cycloheptyl ring fused to

aryl, heteroaryl, or heterocyclyl wherein one, two

or three carbons of the cyclopentyl, cyclohexyl, or

35 cycloheptyl is optionally replaced with a heteroatom
independently selected from NH, NR₂₁₅, O, and S(=O)₀₋₂,

and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group is optionally substituted with one or two groups that are independently R_{205} , $=O$, $-CO-$ $NR_{235}R_{240}$, or $-SO_2-$ (C_1-C_4 alkyl), or

5 C_2-C_{10} alkenyl or C_2-C_{10} alkynyl, each of which is optionally substituted with 1, 2, or 3 independently selected R_{205} groups, wherein

each aryl and heteroaryl is optionally substituted with 1, 2, or 3 R_{200} , and wherein each heterocyclyl is

10 optionally substituted with 1, 2, 3, or 4 independently selected R_{210} ;

R_{200} at each occurrence is independently selected from $-OH$, $-NO_2$, halogen, $-CO_2H$, $C\equiv N$, $-(CH_2)_{0-4}-CO-NR_{220}R_{225}$, $-(CH_2)_{0-4}-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4}-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4}-CO-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-CO-aryl$, $-(CH_2)_{0-4}-CO-heteroaryl$, $-(CH_2)_{0-4}-CO-heterocyclyl$, $-(CH_2)_{0-4}-CO-O-R_{215}$, $-(CH_2)_{0-4}-SO_2-NR_{220}R_{225}$, $-(CH_2)_{0-4}-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4}-SO_2-(C_3-C_7$ cycloalkyl), $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-O-R_{215}$, $-(CH_2)_{0-4}-N(H$ or $R_{215})-CO-N(R_{215})_2$, $-(CH_2)_{0-4}-N(-H$ or $R_{215})-CO-R_{220}$, $-(CH_2)_{0-4}-NR_{220}R_{225}$, $-(CH_2)_{0-4}-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4}-O-P(O)-OR_{240}$, $-(CH_2)_{0-4}-O-CO-N(R_{215})_2$, $-(CH_2)_{0-4}-O-CS-N(R_{215})_2$, $-(CH_2)_{0-4}-O-(R_{215})$, $-(CH_2)_{0-4}-O-(R_{215})-COOH$, $-(CH_2)_{0-4}-S-(R_{215})$, $-(CH_2)_{0-4}-O-(C_1-C_6$ alkyl optionally substituted with 1, 2, 3, or 5 $-F$), C_3-C_7 cycloalkyl, $-(CH_2)_{0-4}-N(H$ or $R_{215})-SO_2-R_{220}$, $-(CH_2)_{0-4}-C_3-C_7$ cycloalkyl,

25 C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 independently selected R_{205} groups,

C_2-C_{10} alkenyl and C_2-C_{10} alkynyl, each of which is

30 optionally substituted with 1 or 2 independently selected R_{205} groups, wherein

the aryl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 groups that are independently R_{205} , R_{210} , or

35 C_1-C_6 alkyl substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} , and wherein

the heterocyclyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{210} ;

R_{205} at each occurrence is independently selected from C_1-C_6

5 alkyl, halogen, -OH, -O-phenyl, -SH, -S- C_1-C_6 alkyl, -C≡N, -CF₃, C_1-C_6 alkoxy, NH₂, NH(C_1-C_6 alkyl) or N-(C_1-C_6 alkyl)(C_1-C_6 alkyl);

R_{210} at each occurrence is independently selected from halogen,

10 C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, -NR₂₂₀R₂₂₅, OH, C≡N, -CO-(C_1-C_4 alkyl), -SO₂-NR₂₃₅R₂₄₀, -CO-NR₂₃₅R₂₄₀, -SO₂-(C_1-C_4 alkyl), =O, or

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_3-C_7 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R_{205} groups;

15 R_{215} at each occurrence is independently selected from C_1-C_6 alkyl, -(CH₂)₀₋₂₋(aryl), C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, and -(CH₂)₀₋₂₋(heteroaryl), -(CH₂)₀₋₂₋(heterocyclyl), wherein

the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R_{205} or R_{210} , and wherein

the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 independently selected R_{210} ;

25 R_{220} and R_{225} at each occurrence are independently selected from -H, - C_3-C_7 cycloalkyl, -(C_1-C_2 alkyl)-(C_{3-C₇} cycloalkyl), -(C_1-C_6 alkyl)-O-(C_1-C_3 alkyl), - C_2-C_6 alkenyl, - C_2-C_6 alkynyl, - C_1-C_6 alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, and - C_1-C_{10} alkyl optionally substituted with -OH, -NH₂ or halogen, wherein

the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 independently selected R_{270} groups

35 R_{235} and R_{240} at each occurrence are independently H, or C_1-C_6 alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently selected from -H, C₁-C₄ alkyl, C₁-C₄ alkylaryl, C₁-C₄ alkylheteroaryl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, and phenyl; or

5 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, -SO₂-, and -NR₂₂₀-;

R₂₅₅ and R₂₆₀ at each occurrence are independently selected from

10 -H, -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-aryl, -(C₁-C₄ alkyl)-heteroaryl, -(C₁-C₄ alkyl)-heterocyclyl, -aryl, -heteroaryl, -heterocyclyl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-aryl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heteroaryl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heterocyclyl, and

15 C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from R₂₀₅, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), wherein

20 each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀, or C₁-C₆ alkyl substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀;

25 R₂₆₅ at each occurrence is independently -O-, -S- or -N(C₁-C₆ alkyl)-;

R₂₇₀ at each occurrence is independently R₂₀₅, halogen C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, NR₂₃₅R₂₄₀, -OH, -C≡N, -CO-(C₁-C₄ alkyl), .SO₂-NR₂₃₅R₂₄₀, -CO-NR₂₃₅R₂₄₀, -SO₂-(C₁-C₄ alkyl), =O, or

30 C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R₂₀₅ groups;

35 R₅, R₆ and R₇, at each occurrence are independently H or

-CO-O- (CH₂)_{n₈}-R₄₋₅ where n₈ is 0 thru 2 and R₄₋₅ is C₁-C₆ alkyl or phenyl; and

R₈ is H or C₁-C₆ alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are independently -H or C₁-C₆ alkyl.

The invention also provides methods for the treatment or prevention of Alzheimer's disease, mild cognitive impairment

10 Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising administration of a therapeutically effective amount of a compound or salt of formula I, to a patient in need thereof.

Preferably, the patient is a human.

20 More preferably, the disease is Alzheimer's disease.

More preferably, the disease is dementia.

The invention also provides pharmaceutical compositions comprising a compound or salt of formula I and at least one pharmaceutically acceptable carrier, solvent, adjuvant or diluent.

25 The invention also provides the use of a compound or salt according to formula I for the manufacture of a medicament.

The invention also provides the use of a compound or salt of formula I for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with

cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

The invention also provides compounds, pharmaceutical compositions, kits, and methods for inhibiting beta-secretase-mediated cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A-beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A-beta peptide.

The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating patients with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those patients who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD, and for treating frontotemporal dementias with parkinsonism (FTDP).

The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention is readily demonstrated, for example, using one or more of the assays described herein or known in the art.

Unless the substituents for a particular formula are expressly defined for that formula, they are understood to carry the definitions set forth in connection with the

preceding formula to which the particular formula makes reference.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those
5 methods.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the invention provides compounds of formula I.

Preferred compounds of formula I include those of formula

5 I-1, i.e., compounds of formula I wherein:

R₅, R₆ and R₇ are each hydrogen.

Preferred compounds of the formula I and formula I-1 include compounds of the formula I-2, i.e., compounds of the formula I or formula I-1 wherein:

10 R₈ is hydrogen.

Preferred compounds of the formula I, formula I-1, and formula I-2, include compounds of the formula I-3, i.e., compounds of the formula I, I-1, or I-2, wherein:

R₂ is aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, or

25 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or

30 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or

35 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH,

-C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo.

5 Preferred compounds of formula I-3 also include those wherein

R₂ is -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, or C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo.

Preferred compounds of formula I-3 also include those wherein

35 R₂ is -(CH₂)-aryl, where the aryl is optionally substituted with 1, 2, 3, or 4 groups independently selected from

halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or dialkylamino, -C(=O)-amino, -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, or

C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or

C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo.

Preferred compounds of formula I-3 also include those wherein

R₂ is -CH₂-phenyl where the phenyl ring is optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, C₁-C₄ alkoxy, hydroxy, -NO₂, and

C₁-C₄ alkyl optionally substituted with 1, 2, or 3 substituents independently selected from halogen, OH, SH, NH₂, NH(C₁-C₆ alkyl), N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), C≡N, CF₃.

Preferred compounds of formula I-3 also include those wherein

R₂ is -CH₂-phenyl where the phenyl ring is optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, hydroxy, -CF₃, and -NO₂.

Preferred compounds of formula I-3 also include those 5 wherein R₂ is benzyl or 3,5-difluorobenzyl.

Preferred compounds of the formula I, formula I-1, and formula I-2, include compounds of the formula I-4, i.e., compounds of the formula I, I-1, or I-2, wherein:

R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups

10 independently selected from halogen, -OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally 15 substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino.

Preferred compounds of formula I-4 also include those

wherein

R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups 20 independently selected from halogen, -OH, =O, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino, mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino and -OC(=O)-mono- or dialkylamino.

Preferred compounds of formula I-4 also include those 25
wherein

R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -SH, -C≡N, C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino, and mono- or dialkylamino.

Preferred compounds of formula I-4 also include those 30
wherein

R₂ is ethyl, n-propyl, iso-propyl, n-butyl, t-butyl or iso-butyl.

Preferred compounds of the formula I, formula I-1, formula 35
I-2, formula I-3, and formula I-4, include compounds of the

formula I-5, i.e., compounds of the formula I, I-1, I-2, I-3, or I-4 wherein:

R₁ is -(CRR')₀₋₆R₁₀₀;

R₁₀₀ represents aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W-heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-heterocyclyl, -CH[(CH₂)₀₋₂O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂O-R₁₅₀]-(CH₂)₀₋₂-heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl, or

R₁₀₀ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is -(C₁-C₆ alkyl)-O-C₁-C₆ alkyl) or -(C₁-C₆ alkyl)-S-(C₁-C₆ alkyl), each of which is optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups.

Preferred compounds of formula I-5 also include compounds wherein

R₁ is -(CRR')₀₋₆R₁₀₀; and

R₁₀₀ represents aryl, heteroaryl, or heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-5 include compounds

wherein

R₁ is -R₁₀₀; and

R₁₀₀ represents aryl, or heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-

O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-5 also include compounds wherein

R₁ is -aryl or -heteroaryl where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl.

Preferred compounds of formula I-5 also include compounds wherein

R₁ is -aryl or -heteroaryl where the ring portions of each are optionally substituted with 1 or 2 groups independently selected from

C₁-C₆ alkyl, halogen, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅.

Preferred compounds of formula I-5 also include compounds wherein

R₁ is -phenyl, or pyridinyl, where the ring portion of each is optionally substituted with 1 or 2 groups independently selected from

5 C₁-C₆ alkyl, halogen, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅.

Preferred compounds of formula I-5 also include compounds wherein

10 R₁ is -phenyl, or pyridinyl, where the ring portion of each is optionally substituted with 1 or 2 groups independently selected from C₁-C₃ alkyl, halogen, -SO₂-NR₁₀₅R'₁₀₅, -CO-NR₁₀₅R'₁₀₅, and -N(R₁₅₀)-SO₂-R₁₀₅, wherein R₁₀₅, R'₁₀₅ and R₁₅₀ are independently H or C₁-C₆ alkyl, or R₁₀₅ and R₁₀₅' together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring.

Preferred compounds of the formula I, formula I-1, formula I-2, formula I-3, formula I-4, and formula I-5 include compounds of the formula I-6, i.e., compounds of the formula I, I-1, I-2, I-3, I-4, or I-5 wherein:

R₃ is H or is

25 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

30 - (CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of

35

R_{205} , $-CO_2H$, $-CO_2-$ (C_1-C_4 alkyl), $-CO-NH_2$, $-CO-NH(C_1-C_6$ alkyl) and $-CO-N-$ (C_1-C_6 alkyl) (C_1-C_6 alkyl).

Preferred compounds of formula I-6 also include compounds wherein

5 R₃ is H or is

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -COOH, -COO(C_1-C_4 alkyl), -CO-NH₂, -CO-NH(C_1-C_6 alkyl), -CO-N-(C_1-C_6 alkyl) (C_1-C_6 alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino.

Preferred compounds of formula I-6 also include compounds wherein

R₃ is H or is C₁-C₃ alkyl.

Preferred compounds of formula I-6 also include compounds wherein R₃ is H or methyl.

Preferred compounds of the formula I, formula I-1, formula I-2, formula I-3, formula I-4, formula I-5, and formula I-6 include compounds of the formula I-7, i.e., compounds of the formula I, I-1, I-2, I-3, I-4, I-5, or I-6 wherein:

R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -
 (CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-heterocyclyl,
 heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-aryl,
 -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-
 heteroaryl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heteroaryl, -
 (CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-aryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-
 (R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂,
 -CH(heterocyclyl)₂, -CH(aryl)(heteroaryl), -(CH₂)₀₋₁-
 CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl, -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-
 (CH₂)₀₋₁-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C₁-
 C₄ alkyl), -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂, (C₁-C₆
 alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂,
 -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀), or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), $-SH$, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$, or $-(CH_2)_{0-3}-(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-CO_2H$, $-CO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH(C_1-C_6$ alkyl) and $-CO-N-(C_1-C_6$ alkyl) (C_1-C_6 alkyl).

Preferred compounds of formula I-7 also include compounds wherein

R_4 is hydrogen, $-(CR_{245}R_{250})_{0-4}$ -aryl, $-(CR_{245}R_{250})_{0-4}$ -heteroaryl, $-(CR_{245}R_{250})_{0-4}$ -heterocyclyl, $-(CR_{245}R_{250})_{0-4}$ -aryl-heteroaryl, $-[C(R_{255})(R_{260})]_{1-3}-CO-N-(R_{255})_2$, $-CH(aryl)_2$, $-CH(heteroaryl)_2$, $-CH(heterocyclyl)_2$, $-CH(aryl)(heteroaryl)$, or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), $-SH$, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$, or $-(CH_2)_{0-3}-(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-CO_2H$, $-CO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH(C_1-C_6$ alkyl) and $-CO-N-(C_1-C_6$ alkyl) (C_1-C_6 alkyl).

Preferred compounds of formula I-7 also include compounds wherein

R_4 is hydrogen, $-(CR_{245}R_{250})_{0-4}$ -aryl, $-(CR_{245}R_{250})_{0-4}$ -heteroaryl, $-(CR_{245}R_{250})_{0-4}$ -heterocyclyl, $-[C(R_{255})(R_{260})]_{1-3}-CO-N-(R_{255})_2$, $-CH(aryl)_2$, or

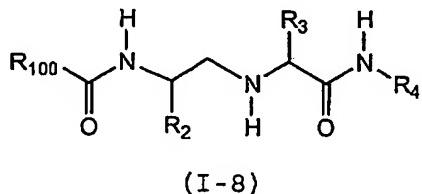
C_1-C_6 alkyl optionally substituted with 1, or 2 groups independently selected from the group consisting of R_{205} , $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), $-SH$, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$.

Preferred compounds of formula I-7 also include compounds wherein R₄ is hydrogen, -[C(R₂₅₅)(R₂₆₀)]-CO-N-(R₂₅₅)₂, or C₁-C₆ alkyl.

Preferred compounds of the formula I-7 also include
5 compounds wherein R₂₅₅ and R₂₆₀ at each occurrence are independently C₁-C₆ alkyl.

Preferred compounds of the formula I, formula I-1, formula I-2, formula I-3, formula I-4, formula I-5, formula I-6, and formula I-7 include compounds of the formula I-8:

10



wherein

R₁₀₀ represents aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-

15 aryl, ., -heteroaryl-W-heteroaryl, -heteroaryl-W- heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-

heteroaryl, -heterocyclyl-W-heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or

20 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋

25 4-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-

(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋

30 4-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl),

-(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀,

-(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-

CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-

O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈

alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋

4-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋

4-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-

N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-

R_{140} , - $(CH_2)_{0-4}-O-CO-(C_1-C_6\text{ alkyl})$, - $(CH_2)_{0-4}-O-P(O)-(O-$
 $R_{110})_2$, - $(CH_2)_{0-4}-O-CO-N(R_{150})_2$, - $(CH_2)_{0-4}-O-CS-N(R_{150})_2$, -
 $(CH_2)_{0-4}-O-(R_{150})$, - $(CH_2)_{0-4}-O-R_{150}'-COOH$, - $(CH_2)_{0-4}-S-$
 (R_{150}) , - $(CH_2)_{0-4}-N(R_{150})-SO_2-R_{105}$, - $(CH_2)_{0-4}-C_3-C_7$
5 cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl, or
 R_{100} is C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 R_{115}
 groups, or
 R_{100} is - $(C_1-C_6\text{ alkyl})-O-C_1-C_6\text{ alkyl}$ or - $(C_1-C_6\text{ alkyl})-S-(C_1-C_6$
10 alkyl), each of which is optionally substituted with 1, 2,
 or 3 R_{115} groups, or
 R_{100} is C_3-C_8 cycloalkyl optionally substituted with 1, 2, or 3
 R_{115} groups;
 R_2 is aryl, heteroaryl, heterocyclyl, - C_1-C_6 alkyl-aryl, - C_1-C_6
15 alkyl-heteroaryl, or - C_1-C_6 alkyl-heterocyclyl, where
 the ring portions of each are optionally substituted
 with 1, 2, 3, or 4 groups independently selected from
 halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -
 N(R)COR', or -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-
 amino, -SO₂-mono or dialkylamino, -C(=O)-amino,
20 -C(=O)-mono or dialkylamino, -SO₂-(C₁-C₄) alkyl, or
 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3
 groups which are independently selected from
 halogen, or
 C_3-C_7 cycloalkyl optionally substituted with 1, 2, or
25 3 groups independently selected from halogen, -
 OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆
 alkyl and mono- or dialkylamino, or
 C_1-C_{10} alkyl optionally substituted with 1, 2, or 3
 groups independently selected from halogen, -OH,
30 -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or
 dialkylamino and -C₁-C₃ alkyl, or
 C_2-C_{10} alkenyl or C_2-C_{10} alkynyl each of which is
 optionally substituted with 1, 2, or 3 groups
 independently selected from halogen, -OH, -SH,
35 -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and
 mono- or dialkylamino; and the heterocyclyl

group is optionally further substituted with
oxo; or

R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
independently selected from -SH, -C≡N, C₁-C₃ alkoxy, -S-

5 (C₁-C₃) alkyl, amino, and mono- or dialkylamino;

R₃ is H or is

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, =O, -COOH,
-COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-

10 N-(C₁-C₆ alkyl) (C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃
alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -
OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or
C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally
substituted with 1, 2, or 3 groups independently

15 selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃
alkoxy, amino, and mono- or dialkylamino, or
-(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is
optionally substituted with 1, 2, or 3 groups

independently selected from the group consisting of
20 R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆
alkyl) and -CO-N-(C₁-C₆ alkyl) (C₁-C₆ alkyl); and

R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -
(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-

25 heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-heterocyclyl,
-(CR₂₄₅R₂₅₀)₀₋₄-aryl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-aryl,
-(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-
heteroaryl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-
heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heterocyclyl, -
(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-aryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-

30 (R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂,
-CH(heterocyclyl)₂, -CH(aryl)(heteroaryl), -(CH₂)₀₋₁-
CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl, -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-
(CH₂)₀₋₁-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C₁-
C₄ alkyl), -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂, (C₁-C₆
alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂,

35 -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀), or

C_1-C_{10} alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-OC=ONR_{235}R_{240}$, $-S(=O)_{0-2}(C_1-C_6$ alkyl), $-SH$, $-NR_{235}C=ONR_{235}R_{240}$, $-C=ONR_{235}R_{240}$, and $-S(=O)_2NR_{235}R_{240}$, or $-(CH_2)_{0-3-}(C_3-C_8)$ cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R_{205} , $-CO_2H$, $-CO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH(C_1-C_6$ alkyl) and $-CO-N-(C_1-C_6$ alkyl) (C_1-C_6 alkyl).

Preferred compounds of the formula I-8 also include compounds wherein:

R_{100} is -aryl or -heteroaryl where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

$-OR$, $-NO_2$, C_1-C_6 alkyl, halogen, $-C\equiv N$, $-OCF_3$, $-CF_3$, $-(CH_2)_{0-4-CO-NR_{105}R'_{105}}$, $-(CH_2)_{0-4-O-(CH_2)_{0-4-CONR_{102}R_{102}'}}$, $-(CH_2)_{0-4-CO-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4-CO-(C_2-C_{12}$ alkenyl), $-(CH_2)_{0-4-CO-(C_2-C_{12}$ alkynyl), $-(CH_2)_{0-4-R_{110}}$, $-(CH_2)_{0-4-R_{120}}$, $-(CH_2)_{0-4-R_{130}}$, $-(CH_2)_{0-4-CO-R_{110}}$, $-(CH_2)_{0-4-CO-R_{120}}$, $-(CH_2)_{0-4-CO-R_{130}}$, $-(CH_2)_{0-4-CO-R_{140}}$, $-(CH_2)_{0-4-CO-O-R_{150}}$, $-(CH_2)_{0-4-SO_2-NR_{105}R'_{105}}$, $-(CH_2)_{0-4-SO-(C_1-C_8$ alkyl), $-(CH_2)_{0-4-SO_2-(C_1-C_{12}$ alkyl), $-(CH_2)_{0-4-N(R_{150})-CO-O-R_{150}}$, $-(CH_2)_{0-4-N(R_{150})-CO-N(R_{150})_2}$, $-(CH_2)_{0-4-N(R_{150})-CO-R_{105}}$, $-(CH_2)_{0-4-NR_{105}R'_{105}}$, $-(CH_2)_{0-4-R_{140}}$, $-(CH_2)_{0-4-O-CO-(C_1-C_6$ alkyl), $-(CH_2)_{0-4-O-CO-N(R_{150})_2}$, $-(CH_2)_{0-4-O-(R_{150})}$, $-(CH_2)_{0-4-N(R_{150})-SO_2-R_{105}}$, $-(CH_2)_{0-4-C_3-C_7$ cycloalkyl, (C_2-C_{10}) alkenyl, or (C_2-C_{10}) alkynyl;

R_2 is $-(CH_2)-$ aryl, where the aryl is optionally substituted with 1, 2, 3, or 4 groups independently selected from

halogen, $-OH$, $-SH$, $-C\equiv N$, $-NO_2$, $-NR_{105}R'_{105}$, $-CO_2R$, $N(R)COR'$, or $-N(R)SO_2R'$, $-C(=O)-(C_1-C_4)$ alkyl, $-SO_2-$ amino, $-SO_2$ -mono or dialkylamino, $-C(=O)-$ amino, $-C(=O)-$ mono or dialkylamino, $-SO_2-(C_1-C_4)$ alkyl, or C_1-C_6 alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen, or

C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino, or

5 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, or

10 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with

15 oxo; or

R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -SH, -C≡N, C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino, and mono- or dialkylamino;

R₃ is H or is

20 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino; and

25 R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-heteroaryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-(R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂, -CH(heterocyclyl)₂,

30 -CH(aryl)(heteroaryl), or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -NR₂₃₅C=ONR₂₃₅R₂₄₀, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀, or

35 -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups

independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl).

Further preferred compounds of the formula I-8 also

5 include compounds wherein:

R₁₀₀ is -aryl or -heteroaryl where the ring portions of each are optionally substituted with 1 or 2 groups independently selected from

C₁-C₆ alkyl, halogen, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-CO-

10 NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅;

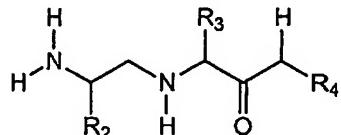
R₂ is -CH₂-phenyl where the phenyl ring is optionally substituted with 1 or 2 groups independently selected from halogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, hydroxy, -CF₃, and -NO₂; or

15 R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from -SH, -C≡N, C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino, and mono- or dialkylamino;

R₃ is H or methyl; and

R₄ is hydrogen, -[C(R₂₅₅)(R₂₆₀)]-CO-N-(R₂₅₅)₂, or C₁-C₆ alkyl.

20 In another aspect, the invention provides compounds of the formula (V):



(V)

wherein R₂, R₃ and R₄ are as defined above for compounds of 25 formula I.

The invention also provides methods for treating a patient who has, or is preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for

treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar
5 hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy
10 body type of Alzheimer's disease and who is in need of such treatment which includes administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salts thereof.

In an embodiment, this method of treatment can be used
15 where the disease is Alzheimer's disease.

In an embodiment, this method of treatment can help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this method of treatment can be used where the disease is mild cognitive impairment.

20 In an embodiment, this method of treatment can be used where the disease is Down's syndrome.

In an embodiment, this method of treatment can be used where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

25 In an embodiment, this method of treatment can be used where the disease is cerebral amyloid angiopathy.

In an embodiment, this method of treatment can be used where the disease is degenerative dementias.

30 In an embodiment, this method of treatment can be used where the disease is diffuse Lewy body type of Alzheimer's disease.

In an embodiment, this method of treatment can treat an existing disease.

35 In an embodiment, this method of treatment can prevent a disease from developing.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration from about 5 0.5 to about 100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration from about 0.5 mg/day to about 200 mg/day; for rectal administration from about 0.5 mg to about 500 mg.

In an embodiment, this method of treatment can employ 10 therapeutically effective amounts: for oral administration from about 1 mg/day to about 100 mg/day; and for parenteral administration from about 5 to about 50 mg daily.

In an embodiment, this method of treatment can employ 15 therapeutically effective amounts for oral administration from about 5 mg/day to about 50 mg/day.

The invention also includes pharmaceutical compositions which include a compound of formula (I) or a pharmaceutically acceptable salts thereof.

The invention also includes the use of a compound of 20 formula (I) or pharmaceutically acceptable salts thereof for the manufacture of a medicament for use in treating a patient who has, or in preventing a patient from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's 25 disease, for treating patients with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch- 30 Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia 35 associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body

type of Alzheimer's disease and who is in need of such treatment.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Alzheimer's disease.

5 In an embodiment, this use of a compound of formula (I) can help prevent or delay the onset of Alzheimer's disease.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is mild cognitive impairment.

10 In an embodiment, this use of a compound of formula (I) can be employed where the disease is Down's syndrome.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

15 In an embodiment, this use of a compound of formula (I) can be employed where the disease is cerebral amyloid angiopathy.

In an embodiment, this use of a compound of formula (I) can be employed where the disease is degenerative dementias.

20 In an embodiment, this use of a compound of formula (I) can be employed where the disease is diffuse Lewy body type of Alzheimer's disease.

In an embodiment, this use of a compound employs a pharmaceutically acceptable salt selected from the group consisting of salts of the following acids hydrochloric, 25 hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, methanesulfonic, $\text{CH}_3\text{-}(\text{CH}_2)_n\text{-COOH}$ where n is 0 thru 4, $\text{HOOC}\text{-}(\text{CH}_2)_n\text{-COOH}$ where n is as defined above, HOOC-CH=CH-COOH , and phenyl-COOH.

30 The invention also includes methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype, or at a corresponding site of an isotype or mutant thereof; for inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease

characterized by beta-amyloid deposits in the brain. These methods each include administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salts thereof.

5 The invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase to an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a compound that
10 inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

15 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10
20 nanomolar or less.

In an embodiment, this method includes exposing said beta-secretase to said compound *in vitro*.

In an embodiment, this method includes exposing said beta-secretase to said compound in a cell.

25 In an embodiment, this method includes exposing said beta-secretase to said compound in a cell in an animal.

In an embodiment, this method includes exposing said beta-secretase to said compound in a human.

The invention also includes a method for inhibiting
30 cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of
35 formula (I), or a pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a cleavage site:
between Met652 and Asp653, numbered for the APP-751 isotype;
between Met 671 and Asp 672, numbered for the APP-770 isotype;
between Leu596 and Asp597 of the APP-695 Swedish Mutation;
5 between Leu652 and Asp653 of the APP-751 Swedish Mutation; or
between Leu671 and Asp672 of the APP-770 Swedish Mutation.

In an embodiment, this method exposes said reaction mixture *in vitro*.

10 In an embodiment, this method exposes said reaction mixture *in a cell*.

In an embodiment, this method exposes said reaction mixture *in an animal cell*.

In an embodiment, this method exposes said reaction mixture *in a human cell*.

15 The invention also includes a method for inhibiting production of amyloid beta peptide (A beta) *in a cell*, including administering to said cell an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

20 In an embodiment, this method includes administering to an animal.

In an embodiment, this method includes administering to a human.

25 The invention also includes a method for inhibiting the production of beta-amyloid plaque *in an animal*, including administering to said animal an effective inhibitory amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

30 In an embodiment, this method includes administering to a human.

The invention also includes a method for treating or preventing a disease characterized by beta-amyloid deposits in the brain including administering to a patient an effective therapeutic amount of a compound of formula (I), or a 35 pharmaceutically acceptable salt thereof.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of less than 50 micromolar.

5 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 micromolar or less.

In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 1 micromolar or less.

10 In an embodiment, this method employs a compound that inhibits 50% of the enzyme's activity at a concentration of 10 nanomolar or less.

15 In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 0.1 to about 1000 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 15 to about 1500 mg/day.

20 In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 1 to about 100 mg/day.

In an embodiment, this method employs a compound at a therapeutic amount in the range of from about 5 to about 50 mg/day.

25 In an embodiment, this method can be used where said disease is Alzheimer's disease.

30 In an embodiment, this method can be used where said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type.

The invention also includes a composition including beta-secretase complexed with a compound of formula (I), or a pharmaceutically acceptable salt thereof.

35 The invention also includes a method for producing a beta-secretase complex including exposing beta-secretase to a compound of formula (I), or a pharmaceutically acceptable salt

thereof, in a reaction mixture under conditions suitable for the production of said complex.

In an embodiment, this method employs exposing *in vitro*.

5 In an embodiment, this method employs a reaction mixture that is a cell.

The invention also includes a component kit including component parts capable of being assembled, in which at least one component part includes a compound of formula I enclosed in a container.

10 In an embodiment, this component kit includes lyophilized compound, and at least one further component part includes a diluent.

15 The invention also includes a container kit including a plurality of containers, each container including one or more unit dose of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In an embodiment, this container kit includes each container adapted for oral delivery and includes a tablet, gel, or capsule.

20 In an embodiment, this container kit includes each container adapted for parenteral delivery and includes a depot product, syringe, ampoule, or vial.

25 In an embodiment, this container kit includes each container adapted for topical delivery and includes a patch, medipad, ointment, or cream.

The invention also includes an agent kit including a compound of formula (I), or a pharmaceutically acceptable salt thereof; and one or more therapeutic agent selected from the group consisting of an antioxidant, an anti-inflammatory, a gamma secretase inhibitor, a neurotrophic agent, an acetyl cholinesterase inhibitor, a statin, an A beta peptide, and an anti-A beta antibody.

30 The invention also includes a composition including a compound of formula (I), or a pharmaceutically acceptable salt thereof; and an inert diluent or edible carrier.

In an embodiment, this composition includes a carrier that is an oil.

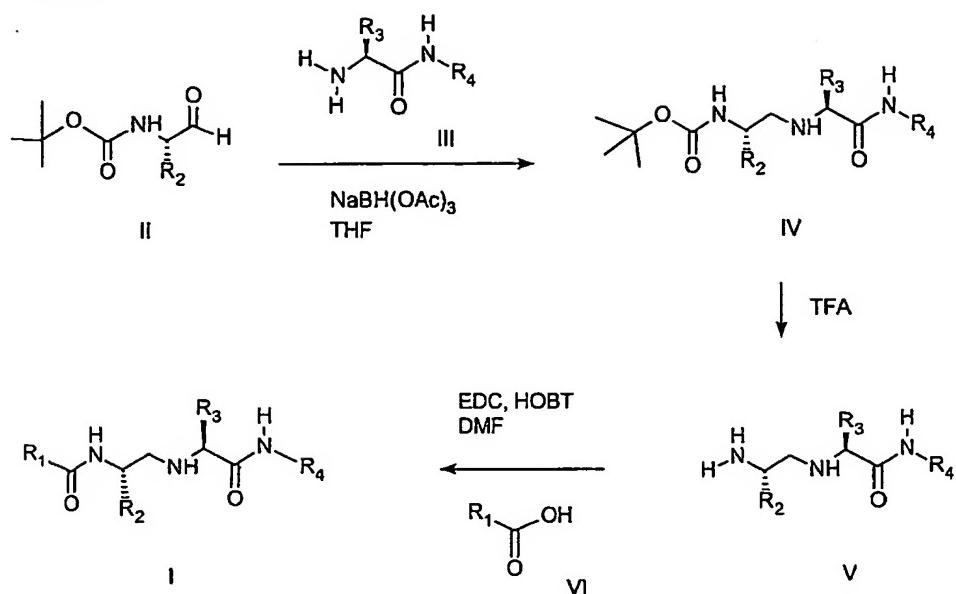
The invention also includes a composition including: a compound of formula (I), or a pharmaceutically acceptable salt thereof; and a binder, excipient, disintegrating agent, lubricant, or gildant.

The invention also includes a composition including a compound of formula (I), or a pharmaceutically acceptable salt thereof; disposed in a cream, ointment, or patch.

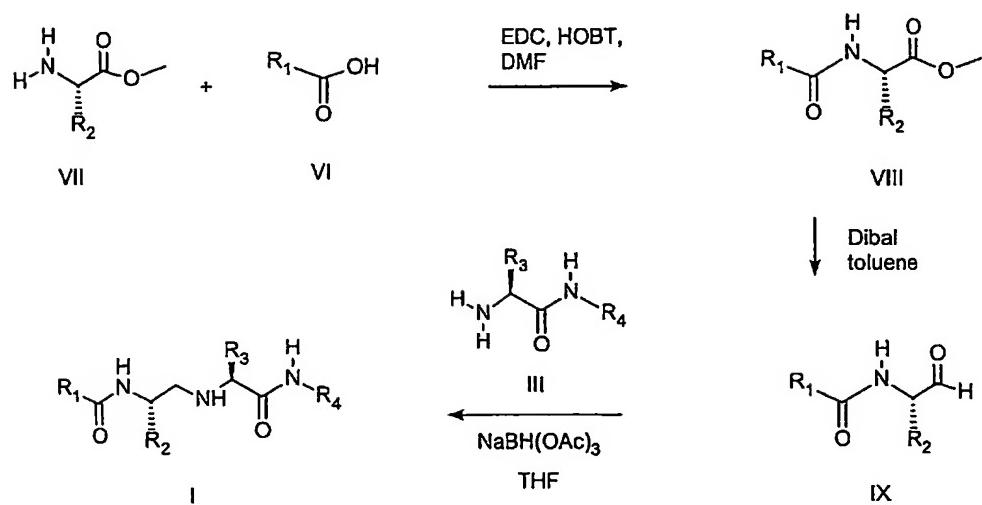
The invention provides compounds of formula (I) that are useful in treating and preventing Alzheimer's disease. The compounds of the invention can be prepared by one skilled in the art based only on knowledge of the compound's chemical structure. The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there is more than one process to prepare the compounds of the invention. Specific examples of methods of preparation can be found in the art. For examples, see *J. Org. Chem.* 1998, 63, 4898-4906; *J. Org. Chem.* 1997, 62, 9348-9353; *J. Org. Chem.* 1996, 61, 5528-5531; *J. Med. Chem.* 1993, 36, 320-330; *J. Am. Chem. Soc.* 1999, 121, 1145-1155; and references cited therein. See also U.S. Patent Nos. 6,150,530, 5,892,052, 5,696,270, and 5,362,912, which are incorporated herein by reference, and references cited therein.

Examples of various processes that can be used to prepare the compounds of the invention are set forth in Schemes 1-4.

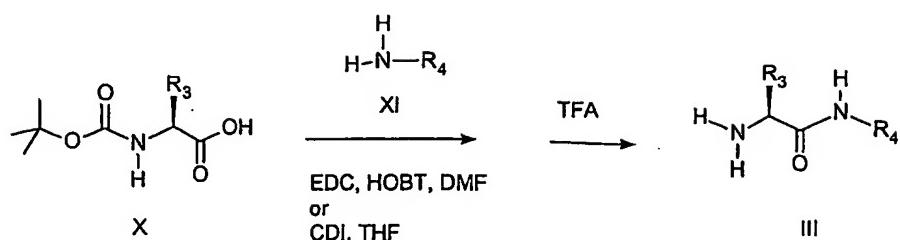
Scheme 1



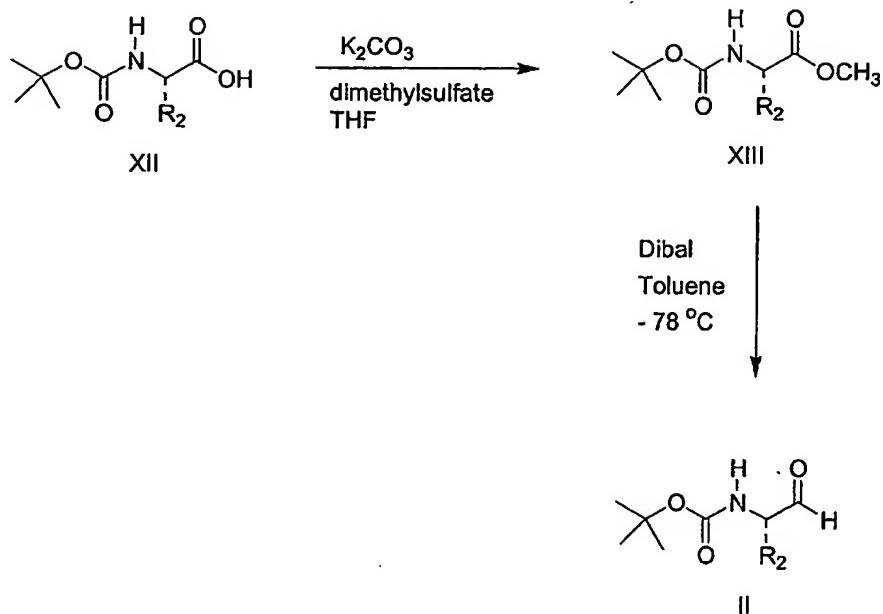
Scheme 2



Scheme 3



SCHEME 4



5

One process to prepare the reduced amides (I) of the present invention is set forth in SCHEME 1. The chemistry is straight forward and in summary is as follows. Aldehydes of 10 Formula II may be condensed with amines of Formula III and reduced to the secondary amines IV with reducing agents such as sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as THF, methanol, or ethylene dichloride, at ambient temperatures to reflux. Boc-protected compounds of 15 Formula IV may be deprotected to the diamines of Formula V with acids such as trifluoroacetic acid in dichloromethane at ambient temperature. Other protecting groups may be removed by

methods known in the art (such as hydrogenation of Cbz groups). Diamines of Formula V can be condensed with carboxylic acids of Formula VI in the presence of condensing reagents such as EDC and HOBT in DMF or other suitable solvent selectively at the 5 primary amino group to afford the reduced amides of Formula I.

Alternatively, the reduced amides (I) of the invention may be prepared as shown in Scheme 2, starting from amino acid esters of Formula VII and carboxylic acids of Formula VI. The methyl ester is used for illustration, but other available 10 esters may be used. These compounds are condensed with an amide coupling agent such as EDC and HOBT in DMF, or other similar reagents well known in the art, to afford compounds of Formula VIII. The esters of Formula VIII may be reduced directly with a reagent such as diisobutylaluminum hydride (Dibal) in toluene 15 at temperatures from -60 to -78 °C to provide the aldehydes of Formula IX. Alternatively, multi-step routes known in the art, as, for example, described in the references cited above, may be used to convert the derivatized amino acid esters of Formula VIII to the aldehydes of Formula IX. Aldehydes of Formula IX 20 may then be condensed with amines of Formula III in the presence of reducing agents such as sodium triacetoxyborohydride or sodium cyanoborohydride in a suitable solvent such as THF, methanol, or ethylene dichloride, at ambient temperatures to reflux, to afford reduced amides of 25 Formula I.

Compounds of Formula II depicted in SCHEME I are aldehydes which are prepared from protected amino acids by procedures described in the literature, for example, Rich, D.H., et. al., *J. Org. Chem.*, 43, 1978, pp 3624-3626; 30 Thompson, W.J., et, al., *J. Med. Chem.* 35, 1992, pp 1685-1701; Jurczak, J. et. al., *Tetrahedron Letters*, 54, 1998, pp 6051-6064. The t-butoxycarbonyl (Boc) protecting group is used for illustration. Other common amino protecting groups known in the art, such as carbobenzoxy (Cbz) may also be used.

35 Scheme 4 illustrates an alternative route to aldehydes of Formula II from commercially available N-protected amino acids

of Formula XII. Acids of Formula XII are converted to esters of Formula XIII by methods well known in the art, such as reaction with dimethylsulfate in the presence of a base such as potassium carbonate in a solvent such as THF. The conversion of 5 esters of Formula XIII to aldehydes of Formula II may be accomplished as described in Rich, D.H., et. al., *J.Org. Chem.* 34, 1978, pp 3624-3626.

Amines of Formula III may be prepared as shown in SCHEME 3. Protected amino acids of Formula X (Boc protection is again 10 used for illustration) may be condensed with amines of Formula XI by means of condensing agents known in the art, such as EDC and HOBT in DMF, or CDI in THF. Boc deprotection with trifluoroacetic acid affords the amine of Formula III. Where the amine of Formula XI is itself an amino acid derivative, 15 such amines may be prepared by condensing the N-protected amino acid with a suitable available amine by these same procedures, followed by N-deprotection (for example, by reaction of a Boc-protected derivative with trifluoroacetic acid) to afford the amine of Formula XI.

The protection of amines is conducted, where appropriate, 20 by methods known to those skilled in the art. Amino protecting groups are known to those skilled in the art. See for example, "Protecting Groups in Organic Synthesis", John Wiley and sons, New York, N.Y., 1981, Chapter 7; "Protecting Groups in Organic 25 Chemistry", Plenum Press, New York, N.Y., 1973, Chapter 2. When the amino protecting group is no longer needed, it is removed by methods known to those skilled in the art. By definition the amino protecting group must be readily removable. A variety of suitable methodologies are known to 30 those skilled in the art; see also T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry", John Wiley and Sons, 1991. Suitable amino protecting groups include t-butoxycarbonyl, benzyl-oxy carbonyl, formyl, trityl, phthalimido, trichloro-acetyl, chloroacetyl, bromoacetyl, 35 iodoacetyl, 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxycarbonyl, 4-ethoxybenzyloxycarbonyl, 4-

fluorobenzylloxycarbonyl, 4-chlorobenzylloxycarbonyl, 3-chlorobenzylloxycarbonyl, 2-chlorobenzylloxycarbonyl, 2,4-dichlorobenzylloxycarbonyl, 4-bromobenzylloxycarbonyl, 3-bromobenzylloxycarbonyl, 4-nitrobenzylloxycarbonyl, 4-cyanobenzylloxycarbonyl, 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenyleth-1-yloxycarbonyl, 1,1-diphenylprop-1-yloxycarbonyl, 2-phenylprop-2-yloxycarbonyl, 2-(*p*-toluyl)prop-2-yloxy-carbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxycarbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)ethoxycarbonyl, 2-(methylsulfonyl)-ethoxycarbonyl, 2-(triphenylphosphino)ethoxycarbonyl, fluorenylmethoxycarbonyl, 2-(trimethylsilyl)ethoxy-carbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzylloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, 4-(decyloxyl)benzylloxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, 9-fluoroenylmethyl carbonate, -CH-CH=CH₂ and phenyl-C(=N)-H.

It is preferred that the protecting group be *t*-butoxycarbonyl (BOC) and/or benzylloxycarbonyl (CBZ), it is more preferred that the protecting group be *t*-butoxycarbonyl. One skilled in the art will recognize suitable methods of introducing a *t*-butoxycarbonyl or benzylloxycarbonyl protecting group and may additionally consult T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry, John Wiley and Sons, 1991 for guidance.

The compounds of the invention may contain geometric or optical isomers as well as tautomers. Thus, the invention includes all tautomers and pure geometric isomers, such as the *E* and *Z* geometric isomers, as well as mixtures thereof. Further, the invention includes pure enantiomers and diastereomers as well as mixtures thereof, including racemic mixtures. The individual geometric isomers, enantiomers or diastereomers may be prepared or isolated by methods known to

those skilled in the art, including but not limited to chiral chromatography; preparing diastereomers, separating the diastereomers and converting the diastereomers into enantiomers through the use of a chiral resolving agent.

5 Compounds of the invention with designated stereochemistry can be included in mixtures, including racemic mixtures, with other enantiomers, diastereomers, geometric isomers or tautomers. In a preferred aspect, compounds of the invention with (S, R, R), (S, S, S), or (S, R, S) stereochemistry are
10 typically present in these mixtures in excess of 50 percent. Preferably, compounds of the invention with designated stereochemistry are present in these mixtures in excess of 80 percent... More preferably, compounds of the invention with designated stereochemistry are present in these mixtures in
15 excess of 90 percent. Even more preferably, compounds of the invention with designated stereochemistry are present in these mixtures in excess of 99 percent.

Several of the compounds of formula (I) are amines, and as such form salts when reacted with acids. Pharmaceutically
20 acceptable salts are preferred over the corresponding amines of formula (I) since they produce compounds which are more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or
25 undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids acetic, aspartic,
30 benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinic, hydrabamic, hydrobromic,
35 hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic,

methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, 5 succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm. Sci.*, 66(1), 1, (1977).

The invention provides compounds, compositions, kits, and 10 methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

15 Methods of the Invention

The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid 20 plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating patients with MCI (mild cognitive impairment) and preventing or delaying the 25 onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and 30 recurrent lobal hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, 35 and diffuse Lewy body type Alzheimer's disease. The compounds and compositions of the invention are particularly useful for

treating or preventing Alzheimer's disease. When treating or preventing these diseases, the compounds of the invention can either be used individually or in combination, as is best for the patient.

5 As used herein, the term "treating" means that the compounds of the invention can be used in humans with at least a tentative diagnosis of disease. The compounds of the invention will delay or slow the progression of the disease thereby giving the individual a more useful life span.

10 The term "preventing" means that the compounds of the invention are useful when administered to a patient who has not been diagnosed as possibly having the disease at the time of administration, but who would normally be expected to develop the disease or be at increased risk for the disease. The
15 compounds of the invention will slow the development of disease symptoms, delay the onset of the disease, or prevent the individual from developing the disease at all. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease due
20 to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids.

In treating or preventing the above diseases, the
25 compounds of the invention are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

30 In treating a patient displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely, as needed. In treating patients who are not diagnosed as having Alzheimer's disease, but who are believed to be at
35 substantial risk for Alzheimer's disease, the physician should preferably start treatment when the patient first experiences

early pre-Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some patients who may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as 5 APOE4 or other biological indicators that are predictive for Alzheimer's disease. In these situations, even though the patient does not have symptoms of the disease, administration of the compounds of the invention may be started before 10 symptoms appear, and treatment may be continued indefinitely to prevent or delay the onset of the disease.

Dosage Forms and Amounts

The compounds of the invention can be administered orally, parenterally, (IV, IM, depo-IM, SQ, and depo SQ), sublingually, 15 intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The 20 compounds are preferably formulated into suitable pharmaceutical preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical 25 compositions using techniques and procedures well known in the art.

About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is compounded with a physiologically acceptable vehicle, carrier, 30 excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably 35 formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30

mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce
5 the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable carrier. Upon mixing or addition of the compound(s), the
10 resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The form of the resulting mixture depends upon a number of factors,
15 including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or condition treated and may be empirically determined.

20 Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active materials can also be mixed with other active materials
25 that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

30 Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the
35 compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are 5 formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but 10 not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration 15 may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for 20 example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. 25 The inhibitor and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the desired mode of administration, including, but 30 not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampoules, vials, and the like for parenteral administration; and patches, medipads, creams, and the like for topical administration.

35 The concentration of active compound in the drug composition will depend on absorption, inactivation, and

excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art.

The active ingredient may be administered at once, or may
5 be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test
10 data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional
15 judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

If oral administration is desired, the compound should be
20 provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in
25 combination with an antacid or other such ingredient.

Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds
30 can be incorporated with excipients and used in the form of tablets, capsules, or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches, and the like can
35 contain any of the following ingredients or compounds of a similar nature: a binder such as, but not limited to, gum

tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to, 5 magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

When the dosage unit form is a capsule, it can contain, in 10 addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component 15 of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active 20 materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, 25 subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial 30 agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. 35 Parenteral preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or

other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), 5 and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropylene glycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to 10 methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers 15 include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for 20 preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or 25 rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral 30 administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained 35 release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the patient 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that 5 the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In 10 addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

In an embodiment, this method of treatment can employ therapeutically effective amounts: for oral administration 15 from about 0.1 mg/day to about 3,000, preferably about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration from about 0.5 to about 500 mg/day, preferably about 100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration 20 from about 0.5 mg/day to about 200 mg/day; for rectal administration from about 0.5 mg to about 500 mg. It is understood that while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

25 Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in 30 U.S. Patent No. 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective 35 amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depot

formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the patients with 5 Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the 10 amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the 15 invention for intranasal administration is the amount described above for IM administration.

The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those 20 skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount described above for IM administration.

The compounds of the invention can be administered topically. When given by this route, the appropriate dosage 25 form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may 30 be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those 35 skilled in the art. When administered by suppository, the

therapeutically effective amount is from about 0.5 mg to about 500 mg.

The compounds of the invention can be administered by implants as is known to those skilled in the art. When 5 administering a compound of the invention by implant, the therapeutically effective amount is the amount described above for depot administration.

Given a particular compound of the invention and a desired dosage form, one skilled in the art would know how to prepare 10 and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating patients 15 with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid 20 angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear 25 palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the conditions listed above. Such 30 agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory agents such as cyclooxygenase II 35 inhibitors; anti-oxidants such as Vitamin E and ginkolides; immunological approaches, such as, for example, immunization

with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082 (Emilieu, 2000, *Arch. Neurol.* 57:454), and other neurotropic agents of the future.

5 In addition, the compounds of formula (I) can also be used with inhibitors of P-glycoprotein (P-gp). P-gp inhibitors and the use of such compounds are known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-10 4179 (1996), International Publications WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor be such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of formula (A). To that end the P-gp inhibitor and the compounds 15 of formula (A) can be administered at the same time, by the same or different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, 20 tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It 25 is to be understood that additional agents will be found that have the same function and therefore achieve the same outcome; such compounds are also considered to be useful.

The P-gp inhibitors can be administered orally, 30 parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp 35 inhibitors is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a patient may be started on one dose, that dose may have to be varied over time as the patient's condition changes.

When administered orally, the P-gp inhibitors can be administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the patient one thru four times daily. It is preferred that the P-gp inhibitors be administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ.

The P-gp inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage

form can be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp inhibitors needed to be administered the patch is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art.

The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

There is nothing novel about the route of administration nor the dosage forms for administering the P-gp inhibitors. Given a particular P-gp inhibitor, and a desired dosage form, one skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds of the invention administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, and other medication the individual may be taking as is well known to administering physicians who are skilled in this art.

30

Inhibition of APP Cleavage

The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). While

not wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide (A beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby 5 cleavage of an APP substrate in the presence of a beta-secretase enzyme is analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an 10 untreated or inactive control is correlated with inhibitory activity. Assay systems that can be used to demonstrate efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the 15 Examples below.

The enzymatic activity of beta-secretase and the production of A beta can be analyzed *in vitro* or *in vivo*, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The 20 analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models expressing native APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the 25 cleavage products, for example, by immunoassay, fluorometric or chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase 30 mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

Beta-Secretase

Various forms of beta-secretase enzyme are known, and are 35 available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native,

recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No. 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Hussain et al., 1999, *Mol. Cell. Neurosci.* 14:419-427; Vassar et al., 1999, *Science* 286:735-741; Yan et al., 1999, *Nature* 402:533-537; Sinha et al., 1999, *Nature* 40:537-540; and Lin et al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant enzyme.

Preferred compounds are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than 50 micromolar, preferably at a concentration of 10 micromolar or less, more preferably 1 micromolar or less, and most preferably 10 nanomolar or less.

20

APP Substrate

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by 5 Kang et al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No.. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-10 234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase 15 cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic 20 APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other 25 detection moiety, a binding substrate, and the like.

Antibodies

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for 30 example, in Pirttila et al., 1999, *Neuro. Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino acids 1-16 of the A beta peptide; antibodies 35 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that are specific for human A beta 1-40 and

1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

10 Assay Systems

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

15

Cell Free Assays

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage

products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

5 Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4 -7, at
10 approximately 37 degrees C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular
15 assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

20 One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in
25 cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This
30 assay is described, for example, in U.S. Patent No 5,942,400.

Cellular Assay

Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A beta.
35 Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor

of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant enzyme as discussed above. The APP substrate may be added to the culture medium and is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed.

Human cell lines that normally process A beta from APP provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of A beta and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of beta-secretase can be measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as A beta.

Although both neural and non-neuronal cells process and release A beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced

processing of APP to A beta, and/or enhanced production of A beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A beta that can be readily measured.

In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to the compound inhibitor, the amount of A beta released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

In vivo Assays: Animal Models

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A beta, as described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos.: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5,811,633, and in Ganes et al., 1995, *Nature* 373:523.

Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compounds. Administration of the

compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at 5 the beta-secretase cleavage site and of A beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A beta from the substrate, the compounds of the invention are effective to 10 reduce beta-secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A beta. Where such contacting is the administration 15 of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where such administration is to a human subject, the 20 compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, to slow 25 the progression of AD in the, and/or to prevent onset or development of AD in a patient at risk for the disease.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All 30 patents and publications referred to herein are hereby incorporated by reference for all purposes.

Definitions

The definitions and explanations below are for the terms 35 as used throughout this entire document including both the specification and the claims.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

The symbol "--" in general represents a bond between two atoms in the chain. Thus CH₃-O-CH₂-CH(R_i)-CH₃ represents a 2-substituted-1-methoxypropane compound. In addition, the symbol "--" represents the point of attachment of the substituent to a compound. Thus for example aryl(C₁-C₆)alkyl- indicates an alkylaryl group, such as benzyl, attached to the compound at the alkyl moiety.

Where multiple substituents are indicated as being attached to a structure, it is to be understood that the substituents can be the same or different. Thus for example "R_m optionally substituted with 1, 2 or 3 R_q groups" indicates that R_m is substituted with 1, 2, or 3 R_q groups where the R_q groups can be the same or different.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A beta. Human beta-secretase is described, for example, in WO00/17369.

Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the patient from a pharmacological/toxicological point of view and to the

manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

A therapeutically effective amount is defined as an amount 5 effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

By "alkyl" and "C₁-C₆ alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon 10 atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. It is understood that in cases where an alkyl chain of a substituent (e.g. of an alkyl, alkoxy or alkenyl group) is shorter or longer than 6 15 carbons, it will be so indicated in the second "C" as, for example, "C₁-C₁₀" indicates a maximum of 10 carbons.

By "alkoxy" and "C₁-C₆ alkoxy" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, attached through at least one divalent oxygen atom, such 20 as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

25 "Alkenyl" and "C₂-C₆ alkenyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and from one to three double bonds and includes, for example, ethenyl, propenyl, 1-but-3-enyl, 1-pent-3-enyl, 1-hex-5-enyl and the like.

30 "Alkynyl" and "C₂-C₆ alkynyl" means straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and one or two triple bonds and includes ethynyl, propynyl, butynyl, pentyn-2-yl and the like.

As used herein, the term "cycloalkyl" refers to saturated 35 carbocyclic radicals having three to twelve carbon atoms. The cycloalkyl can be monocyclic, or a polycyclic fused system.

Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The cycloalkyl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such cycloalkyl groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl.

By "aryl" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl), which is optionally mono-, di-, or trisubstituted. Preferred aryl groups of the present invention are phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, tetralinyl or 6,7,8,9-tetrahydro-5H-benzo[a]cycloheptenyl. The aryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such aryl groups may be optionally substituted with, for example, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, -COOH, -C(=O)O(C₁-C₆ alkyl), -C(=O)NH₂, -C(=O)N(mono- or di-C₁-C₆ alkyl), -S(C₁-C₆ alkyl), -SO₂(C₁-C₆ alkyl), -O-C(=O)(C₁-C₆ alkyl), -NH-C(=O)-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-C(=O)-(C₁-C₆ alkyl), -NH-SO₂-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-SO₂-(C₁-C₆ alkyl), -NH-C(=O)NH₂, -NH-C(=O)N(mono- or di-C₁-C₆ alkyl), -NH(C₁-C₆ alkyl)-C(=O)-NH₂ or -NH(C₁-C₆ alkyl)-C(=O)-N-(mono- or di-C₁-C₆ alkyl).

By "heteroaryl" is meant one or more aromatic ring systems of 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur.

Preferred heteroaryl groups of the present invention include pyridinyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, 5 isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxazolopyridinyl, imidazopyridinyl, isothiazolyl, naphthyridinyl, cinnolinyl, carbazolyl, beta-10 carbolinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, phenoxazinyl, phenothiazinyl, 15 pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, coumarinyl, isocoumarinyl, chromonyl, chromanonyl, pyridinyl-N-oxide, tetrahydroquinolinyl, dihydroquinolinyl, 20 dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl N-oxide, pyrimidinyl N-oxide, pyridazinyl N-oxide, pyrazinyl N-oxide, quinolinyl N-oxide, indolyl N-oxide, indolinyl N-oxide, isoquinolyl N-oxide, 25 quinazolinyl N-oxide, quinoxalinyl N-oxide, phthalazinyl N-oxide, imidazolyl N-oxide, isoxazolyl N-oxide, oxazolyl N-oxide, thiazolyl N-oxide, indolizinyl N-oxide, indazolyl N-oxide, benzothiazolyl N-oxide, benzimidazolyl N-oxide, pyrrolyl N-oxide, oxadiazolyl N-oxide, thiadiazolyl N-oxide, triazolyl N-oxide, 30 tetrazolyl N-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. The heteroaryl groups herein are unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heteroaryl groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-

C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl or di(C₁-C₆)alkylamino(C₁-C₆)alkyl, -COOH, -C(=O)O(C₁-C₆ alkyl), -C(=O)NH₂, -C(=O)N(mono- or di-C₁-C₆ alkyl), -S(C₁-C₆ alkyl), -SO₂(C₁-C₆ alkyl), -O-C(=O)(C₁-C₆ alkyl), -NH-C(=O)-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-C(=O)-(C₁-C₆ alkyl), -NH-SO₂-(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)-SO₂-(C₁-C₆ alkyl), -NH-C(=O)NH₂, -NH-C(=O)N(mono- or di-C₁-C₆ alkyl), -NH(C₁-C₆ alkyl)-C(=O)-NH₂ or -NH(C₁-C₆ alkyl)-C(=O)-N-(mono- or di-C₁-C₆ alkyl).

By "heterocycle", "heterocycloalkyl" or "heterocyclyl" is meant one or more carbocyclic ring systems of 3-, 4-, 5-, 6-, or 7-membered rings which includes fused ring systems of 9-11 atoms containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Preferred heterocycles of the present invention include morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperazinyl, homopiperazinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, azepanyl, diazepanyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. The heterocycle groups herein maybe unsubstituted or, as specified, substituted in one or more substitutable positions with various groups. For example, such heterocycle groups may be optionally substituted with C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, amino(C₁-C₆)alkyl, mono(C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl or =O.

All patents and publications referred to herein are hereby incorporated by reference for all purposes.

Structures were named using Name Pro IUPAC Naming Software, version 5.09, available from Advanced Chemical Development, Inc., 90 Adelaide Street West, Toronto, Ontario, M5H 3V9, Canada.

5 The present invention may be better understood with reference to the following examples. These examples are intended to be representative of specific embodiments of the invention, and are not intended as limiting the scope of the invention.

10

CHEMISTRY EXAMPLES

The following abbreviations may be used in the Examples:

EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or the hydrochloride salt);

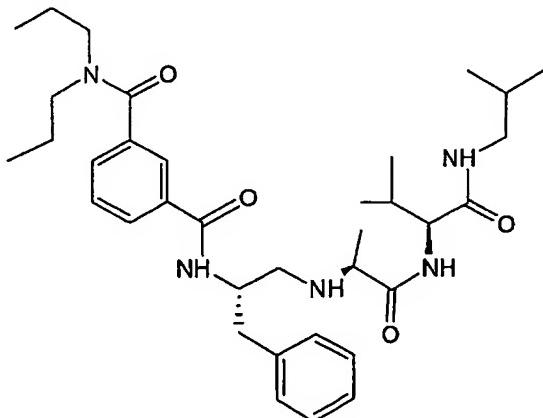
15 DIEA (diisopropylethylamine);

PyBOP (benzotriazol-1-yloxy)tritypyrrolidinophosphonium hexafluorophosphate);

HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate);

20 DCM (dichloromethane).

EXAMPLE 1. Preparation of *N*-[(2*S*)-2-((3-[(dipropylamino)carbonyl]-benzoyl}amino)-3-phenylpropyl]-L-alanyl-*N*^t-isobutyl-L-valinamide



25 Preparation of *N*-t-butoxycarbonylphenylalanal

N-t-butoxycarbonylphenylalanine methyl ester (1.0 g, 3.6 mmol) is dissolved in toluene (15 mL) and the solution is

placed under nitrogen and cooled to - 78 °C. To the stirred solution is added, dropwise over 5 min, 9.0 mL of a 1 M solution of Dibal (diisobutylaluminum hydride) in toluene. After 1 h, 1 mL of methanol is added dropwise, and the solution 5 is poured into an aqueous solution of Rochelle salts (potassium sodium tartrate) cooled in an ice bath. The mixture is stirred for 2 h and the organic material is extracted into ethyl ether. The organic phase is washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to a colorless oil. 10 This is chromatographed over silica gel, eluting with 20% ethyl acetate in heptane, to afford 0.8 g (3.2 mmol, 88%) of the title compound as a white solid. NMR (CDCl_3) δ 9.6 (s, 1H), 7.33-7.16 (m, 5H), 5.03 (b d, 1H), 4.43 (q, $J = 7$ Hz, 1 H), 3.12 (d, $J = 7$ Hz, 2H), 1.43 (s, 9H).

15

Preparation of N^2 -*(tert*-butoxycarbonyl)- N^1 -isobutyl-L-valinamide

N-t-butoxycarbonylvaline (2.2 g, 10 mmol) is dissolved in dry THF under nitrogen, and to this is added 2.0 g (12 mmol) of carbonyldiimidazole. After this mixture is stirred for 50 min, 20 2.0 mL (20 mmol) of isobutylamine is added. After 1 week, the mixture is concentrated, dissolved in ethyl acetate, and washed successively with aqueous potassium hydrogen sulfate, water, and brine. It is dried over anhydrous sodium sulfate and 25 concentrated to 2.27 g (8.3 mmol, 83%) of the title compound as a white solid. NMR (CDCl_3) δ 6.0 (br, 1H), 5.07 (br d, 1H), 3.83 (m, 1H), 3.10 (m, 2H), 2.14 (m, 1H), 1.77 (m, 1H), 1.44 (s, 9H), 1.01-0.90 (overlapping d, 12H). HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{28}\text{N}_2\text{O}_3+\text{H}_1$ 273.2178, found 273.2180

30

Preparation of N -*(tert*-butoxycarbonyl)-L-alanyl- N^1 -isobutyl-L-valinamide

N^2 -*(tert*-butoxycarbonyl)- N^1 -isobutyl-L-valinamide (1.62 g, 5.95 mmol) is stirred with 6 mL of trifluoroacetic acid in 35 10 mL of dichloromethane for 1 h, and then concentrated on a rotary evaporator. Meanwhile N-t-butoxycarbonylalanine (1.23 g,

6.5 mmol) is combined with EDC (1.25 g, 6.5 mmol) and HOBT (0.88 g, 6.5 mmol) in 10 mL of DMF, and this mixture is allowed to stir under nitrogen for 1 h. Then the concentrated amine is dissolved in 5 mL of DMF, and 2.0 mL (18 mmol) of N-methylmorpholine is added. The DMF solution resulting from N-t-butoxycarbonylalanine, EDC, and HOBT is then added to the amine solution, and the mixture is allowed to stir under nitrogen for 3 days. It is quenched with aqueous potassium hydrogen sulfate and diluted with ethyl acetate. The organic phase is washed successively with water, aqueous sodium bicarbonate, and brine, and dried over anhydrous sodium sulfate. Concentration affords a white solid, which is triturated with ethyl ether to remove residual DMF, and then evaporated to yield 1.5 g (4.37 mmol, 73%) of the title compound. NMR (CDCl_3) δ 6.70 (d, J = 9 Hz, 1H), 6.32 (br, 1H), 5.0 (br d, 1H), 4.2 (m, 1H), 4.13 (m, 1H), 3.08 (m, 2H), 2.26 (m, 1H), 1.79 (m, 1H), 1.45 (s, 9H), 1.37 (d, J = 7 Hz, 3H), 0.96-0.89 (overlapping d, 12H). MS (CI) m/z 344 (MH^+)

20 **Preparation of L-alanyl-N¹-isobutyl-L-valinamide**
N-(tert-butoxycarbonyl)-L-alanyl-N¹-isobutyl-L-valinamide (247 mg, 0.72 mmol) is stirred for 30 min under nitrogen with 1 mL of trifluoroacetic acid and 3 mL of dichloromethane. It is concentrated on a rotary evaporator. To the residue is added 2 mL of saturated sodium bicarbonate (pH = 8). The product is diluted with 100 mL of ethyl ether. The aqueous salt is siphoned out and anhydrous sodium sulfate is added. The solution is filtered through glass wool and concentrated to 136 mg of the title compound as an off-white solid. NMR ($\text{MeOD}-d_3$) δ 4.66 (bs) 4.16 (d, J = 8 Hz, 1H), 4.00 (q, J = 7 Hz, 1H), 3.07 (dd, 1H), 2.98 (dd, 1H), 2.05 (m, 1H), 1.79 (m, 1H), 1.49 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 6 H) 0.93 (d, J = 7 Hz, 6H). HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{25}\text{N}_3\text{O}_2+\text{H}_1$ 244.2025, found 244.2023.

35 **Preparation of N-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl]-L-alanyl-N¹-isobutyl-L-valinamide**

N-t-butoxycarbonylphenylalalanal (105 mg, 0.42 mmol) and L-alanyl-N¹-isobutyl-L-valinamide (102 mg, 0.42 mmol) are combined with sodium triacetoxyborohydride (140 mg, 0.66 mmol) in 4 mL of 1,2-dichloroethane and 4 mL of THF containing 0.04 mL (0.66 mmol) of acetic acid. Several mL of methanol are introduced, and the mixture is allowed to stir overnight. The reaction is quenched with aqueous sodium bicarbonate and the product is taken up in 70 mL of ethyl acetate and several mL of methanol. The organic phase is washed with more bicarbonate, and then 10 with brine, and dried over anhydrous sodium sulfate. It is concentrated to a colorless oil, which is chromatographed over silica gel, eluting with 2% to 5 % methanol in dichloromethane. The product-containing fraction is concentrated to afford 84 mg (0.176 mmol, 42%) of the title product as a white solid. NMR (CDCl₃) δ 7.76 (br d, 1H), 7.3-7.17 (m, 5 H), 6.40 (br m, 1H), 4.8 (br d, 1H), 4.13 (dd, 1H), 3.87 (m, 1H), 3.1 (m, 2H), 3.0 (m, 1H), 2.9-2.7 (m, 3H), 2.62 (dd, 1H), 2.15 (m, 1H), 1.76 (m, 1H), 1.39 (s, 9H), 1.27 (d, J = 7 Hz, 3H), 0.96-0.89 (overlapping d, 12H).

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Preparation of N-[(2S)-2-amino-3-phenylpropyl]-L-alanyl-N¹-isobutyl-L-valinamide

N-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropyl]-L-alanyl-N¹-isobutyl-L-valinamide (84 mg, 0.176 mmol) is stirred 25 with 1 mL of trifluoroacetic acid and 3 mL of dichloromethane for 30 min. It is then concentrated on a rotary evaporator and then neutralized with several mL of saturated aqueous sodium bicarbonate. The product is taken up in 70 mL of ethyl ether, washed with several more mL of bicarbonate solution, and then 30 dried over anhydrous sodium sulfate. Concentration from ethyl ether, and then from absolute ethanol, afforded 75 mg of a slightly yellow oil, whose NMR spectrum was consistent with the title compound, along with a small amount of residual ethanol. NMR (CDCl₃) δ 7.96 (d, J = 9 Hz, 1H), 7.3-7.17 (m, 5 H), 6.88 35 (br t, 1H), 4.13 (m, 1H), 3.27 (m, 1H), 3.13 (m, 1H), 3.05 (m, 1 H), 2.94 (m, 1H), 3.83 (m, 2 H), 2.7 (dd, 1H), 2.57 (dd, 1H),

2.08 (m, 1H), 1.72 (m, 1H), 1.31 (d, J = 7 Hz, 3H), 0.93-0.86 (overlapping d, 12H).

Preparation of N-[(2S)-2-(3-[(dipropylamino)carbonyl]-

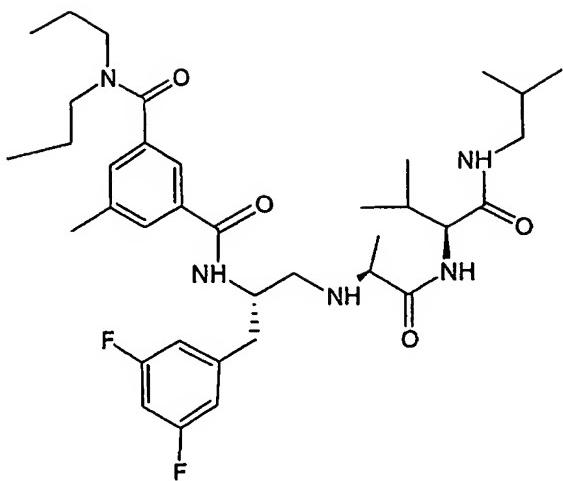
5 benzoyl]amino)-3-phenylpropyl]-L-alanyl-N¹-isobutyl-L-valinamide.

3-[(Dipropylamino)carbonyl]benzoic acid, (52 mg, 0.21 mmol) is combined with EDC (40 mg, 0.21 mmol) and HOBT (30 mg, 0.22 mmol) in 2.5 mL of DMF and stirred under nitrogen for 1 h. This solution is then added to a solution of N-[(2S)-2-amino-3-phenylpropyl]-L-alanyl-N¹-isobutyl-L-valinamide (0.17 mmol) in 1 mL of DMF. The reaction is continued for 3 days at ambient temperature. It is then quenched with 1 N KH₂PO₄ and diluted with ethyl acetate. The organic phase is washed with water, 1 N NaHCO₃, and brine, and dried over Na₂SO₄. Concentration and chromatography over silica gel, eluting with 5% methanol in dichloromethane, affords 53 mg (0.087 mmol, 51%) of the title compound. Addition of several drops of deuterated methanol to the compound in deuterated chloroform is necessary. NMR (CDCl₃+MeOD) δ 7.79 (br d, 1H), 7.69 (s, 1H), 7.44 (m, 2 H), 7.30 (m, 4H), 7.26 (m, obscured by CHCl₃), 7.19 (m, 2H), 4.33 (m, 1H), 4.03 (d, J = 8 Hz, 1H), 3.5-3.4 (m, 3H), 3.13- 3.0 (m, 6H), 2.90 (m, 1 H), 2.68 (dd, 1H), 2.0 (m, 1H), 1.8-1.7 (m, 3H), 1.5 (m, 2H), 1.31 (d, J = 7 Hz, 3H), 0.99 (t, J = 7 Hz, 3H), 0.93-0.86 (overlapping d, 12H), 0.72 (t, J = 7 Hz, 3H). MS (FAB) m/z 608 (MH⁺).

EXAMPLE 2. Preparation of N-[(2S)-3-(3,5-difluorophenyl)-

2-(3-[(dipropylamino)carbonyl]-5-methylbenzoyl]amino)propyl]-

30 L-alanyl-N¹-isobutyl-L-valinamide



Preparation of N-t-butoxycarbonyl(3,5-difluorophenyl)alanine methyl ester

N-t-butoxycarbonyl(3,5-difluorophenyl)alanine (2.6 g, 8.6 mmol) in 35 mL of dry THF under nitrogen is stirred with 2.0 g (14.5 mmol) of pulverized K_2CO_3 and 1.0 mL (10.5 mmol) of dimethylsulfate at 40 °C for 17 h. The mixture is diluted with ethyl acetate, washed twice with 1 N KH_2PO_4 , once with 1 N $NaHCO_3$, twice with water, and finally with brine. The organic phase is dried with Na_2SO_4 and concentrated to a sticky solid. Trituration with heptane affords 2.32 g (7.4 mmol, 85%) of N-t-butoxycarbonyl(3,5-difluorophenyl)alanine methyl ester as a white solid. 1H NMR ($CDCl_3$) δ 6.72-6.56 (m, 3 H), 5.04 (d, J = 8 Hz, 1 H), 4.57 (q, J = 6 Hz, 1 H), 3.75 (s, 3 H), 3.14 (dd, J = 6, 14 Hz, 1 H), 3.01 (dd, J = 6, 14 Hz, 1 H), 1.43 (s, 9 H).

Preparation of N-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propyl]-L-alanyl-N¹-isobutyl-L-valinamide

N-t-Butoxycarbonyl(3,5-difluorophenyl)alanine methyl ester (1.3 g, 4.1 mmol) in toluene (20 mL) is placed under nitrogen and cooled to - 78 °C. To the stirred solution is added, dropwise over 10 min, 12.0 mL of a 1 M solution of Dibal in toluene. After 1 h, 2 mL of methanol is added dropwise, and the solution is poured into an aqueous solution of Rochelle salts and cooled in an ice bath. The mixture is stirred and the organic material is extracted into ethyl ether. The organic phase is

washed with water and brine, dried over Na_2SO_4 , and concentrated to N-t-butoxycarbonyl(3,5-difluorophenyl) alanal as a white solid, 1.2 g (quantitative). N-t-Butoxycarbonyl(3,5-difluorophenyl)alanal (700 mg, 2.45 mmol) and L-alanyl-N¹-isobutyl-L-valinamide (EXAMPLE 1, 700 mg, 2.87 mmol) are combined with sodium triacetoxyborohydride (1.0 g, 4.7 mmol) in 14 mL of THF containing 0.30 mL (5.0 mmol) of acetic acid. The mixture is allowed to stir 18 h. The reaction is quenched with 1 N NaHCO_3 and the product is taken up in 200 mL of ethyl acetate and several mL of methanol. The organic phase is washed with more bicarbonate, and then with brine, and dried over Na_2SO_4 . It is concentrated to a solid, which is chromatographed over silica gel, eluting with 25% to 30% acetone in dichloromethane. The product-containing fractions are concentrated to afford 432 mg (0.84 mmol, 34%) of the title product as a white solid. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{42}\text{F}_2\text{N}_4\text{O}_4+\text{H}_1$ 513.3252, found 513.3259.

Preparation of N-[(2S)-2-amino-3-(3,5-

20 difluorophenyl)propyl]-L-alanyl-N¹-isobutyl-L-valinamide
N-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propyl]-L-alanyl-N¹-isobutyl-L-valinamide (377 mg, 0.735 mmol) is stirred with 1.5 mL of trifluoroacetic acid and 3 mL of dichloromethane for 25 min. It is then concentrated on a rotary evaporator and then neutralized with several mL of saturated aqueous sodium bicarbonate. The product is taken up in ethyl ether containing about 1% methanol, washed with several more mL of bicarbonate solution and with brine, and then dried over Na_2SO_4 . Concentration afforded a quantitative yield of the title compound as a yellow solid. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{34}\text{F}_2\text{N}_4\text{O}_2+\text{H}_1$ 413.2728, found 413.2730.

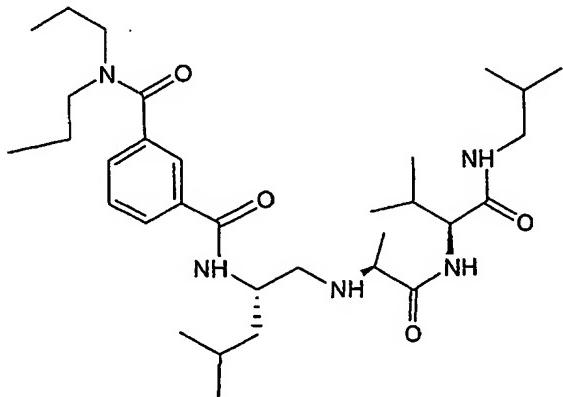
Preparation of N-[(2S)-3-(3,5-difluorophenyl)-2-{[3-

35 [(dipropylamino) carbonyl]-5-methylbenzoyl}amino)propyl]-L-alanyl-N¹-isobutyl-L-valinamide

3-[(Dipropylamino)carbonyl]-5-methylbenzoic acid, (90 mg, 0.34 mmol) is combined with EDC (65 mg, 0.34 mmol) and HOBT (46 mg, 0.34 mmol) in 3 mL of DMF and stirred under nitrogen for 1 h. This solution is then added to a solution of N-[(2S)-2-amino-3-(3,5-difluorophenyl)propyl]-L-alanyl-N¹-isobutyl-L-valinamide (88 mg, 0.21 mmol) in 1 mL of DMF. The reaction is continued for 3 days at ambient temperature. It is then quenched with 1 N KH₂PO₄ and diluted with ethyl acetate containing about 1% of methanol. The organic phase is washed with water, 1 N NaHCO₃, and brine, and dried over Na₂SO₄. Concentration and chromatography over silica gel, eluting with 4% to 6% methanol in dichloromethane, affords 96mg (0.146 mmol, 69%) of the title compound as a light tan solid. ¹H NMR (CDCl₃) δ 7.75 (d, J = 9 Hz, 1 H), 7.54 (s, 1 H), 7.37 (s, 1 H), 7.21 (s, 1 H), 7.16 (d, J = 8 Hz, 1 H), 6.84 (m, 2 H), 6.70 (m, 1 H), 6.64 (m, 1 H), 4.19 (dd, J = 7, 9 Hz, 1 H), 4.05 (m, 1 H), 3.5-3.4 (m, 2 H), 3.33 (dd, J = 6, 14 Hz, 1 H), 3.19-3.02 (m, 5 H), 2.88 (dd, J = 6, 14 Hz, 1 H), 2.68 (dd, J = 4, 13.5 Hz, 1 H), 2.58 (m, 1 H), 2.37 (s, 3 H), 1.96 (m, 1 H), 1.75-1.64 (m, 4 H), 1.50 (m, 2 H), 1.35 (d, J = 7 Hz, 3 H), 0.99 (t, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 0.86 (m, 9 H), 0.71 (t, J = 7 Hz, 3 H).

MS (CI) m/z 658 (MH⁺).

EXAMPLE 3. Preparation of N-[(2S)-2-({3-[(dipropylamino)carbonyl]benzoyl}amino)-4-methylpentyl]-L-alanyl-N¹-isobutyl-L-valinamide



Preparation of Methyl (2S)-2-({3-[(dipropylamino)carbonyl]benzoyl}amino)-4-methylpentanoate

3-[(Dipropylamino)carbonyl]benzoic acid, (1.24 g, 5 mmol)

5 is combined with EDC (0.95 g, 5 mmol) and HOBT (0.69, 5.1 mmol) in 10 mL of DMF and stirred under nitrogen for 1 h. This solution is then added to a solution of L-leucine methyl ester hydrochloride (0.9 g, 5 mmol) and 0.55 mL (5 mmol) of 4-methylmorpholine in 5 mL of DMF. The reaction is continued for 10 3 days at ambient temperature. It is then quenched with 1 N KH₂PO₄ and diluted with ethyl acetate. The organic phase is washed with water, 1 N NaHCO₃, and brine, and dried over Na₂SO₄. Concentration and chromatography over silica gel, eluting with 50% ethyl acetate in heptane, affords 1.65 g (4.4 mmol, 88%) 15 of the title compound as a colorless oil which crystallizes on standing. ¹H NMR (CDCl₃) δ 7.82 (m, 1 H), 7.77 (s, 1 H), 7.51-7.44 (m, 2 H), 6.65 (d, J = 8 Hz, 1 H), 4.84 (m, 1 H), 3.77 (s, 3 H), 3.46 (br t, 2 H), 3.14 (br t, 2 H), 1.78-1.65 (m, 5 H), 1.53 (m, 2 H), 0.99 (m, 9 H), 0.75 (br t, 3 H).

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Preparation of (2S)-2-({3-[(dipropylamino)carbonyl]benzoyl}amino)-4-methylpentanal

Methyl (2S)-2-({3-[(dipropylamino)carbonyl]

benzoyl}amino)-4-methylpentanoate (1.65 g, 4.4 mmol) in 20 mL

25 of toluene under nitrogen is cooled to -78°C. To this is added, dropwise over 5 min, 11 mL of a 1 M solution of Dibal in

toluene. The mixture is stirred at room temperature for 30 minutes and is then quenched by addition of 2 mL of methanol. The cold bath is removed and 20 mL of a Rochelle salt solution is added and vigorously stirred while the mixture warms to ambient

temperature. The product is extracted into ether and the organic phase is washed successively with Rochelle salt

solution, water, and brine. It is dried over Na₂SO₄,

concentrated, and chromatographed over silica gel, eluting with

50% ethyl acetate in heptane, to afford the title compound as a

colorless oil (0.79 g, 2.3 mmol, 52%). ¹H NMR (CDCl₃) δ 9.7 (s,

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35

1 H), 7.85 (m, 1 H), 7.79 (s, 1 H), 7.49 (m, 2 H), 6.81 (d, J = 7 Hz, 1 H), 4.78 (m, 1 H), 3.46 (br t, 2 H), 3.15 (br t, 2 H), 1.82 (m, 2 H), 1.70 (m, 2 H), 1.62-1.53 (m, 3 H), 1.01 (m, 9 H), 0.75 (br t, 3 H).

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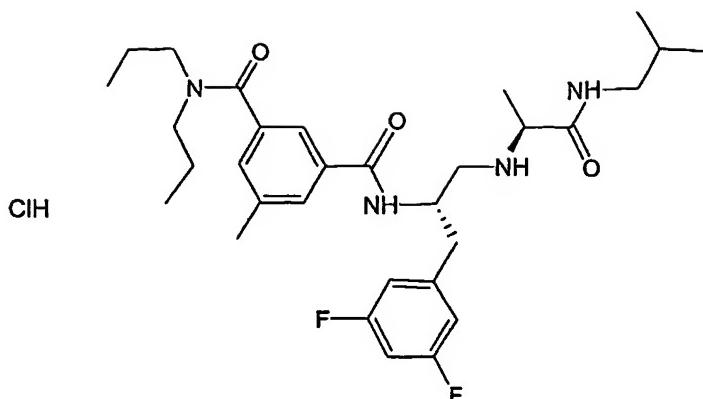
Preparation of N-[(2S)-2-(3-[(dipropylamino)carbonyl]benzoyl)amino]-4-methylpentyl-L-alanyl-N¹-isobutyl-L-valinamide

A solution of (2S)-2-(3-[(dipropylamino)carbonyl]benzoyl)amino)-4-methylpentanal

(290 mg, 0.84 mmol) in 6 mL of dry THF is added to L-alanyl-N¹-isobutyl-L-valinamide (**EXAMPLE 1**, 205 mg, 0.84 mmol) under nitrogen. To this is added 0.12 mL of acetic acid and sodium triacetoxyborohydride (300 mg, 1.41 mmol), and the mixture is stirred for 3 days. Methanol (1 mL) is added. And the mixture is stirred for 3 more hours. It is diluted with 150 mL of ethyl acetate and 5 mL of methanol, and the organic phase is washed successively with 15 mL of 1 N NaHCO₃, water, and brine. The solution is dried with Na₂SO₄, concentrated, and chromatographed over silica gel. Elution with 4% methanol in dichloromethane, followed by 8% methanol in dichloromethane, afforded the title compound as a white solid (154 mg, 0.27 mmol, 32%). ¹H NMR (CDCl₃) δ 7.88 (m, 1 H), 7.78 (m, 2 H), 7.44 (m, 2 H), 7.00 (d, J = 8 Hz, 1 H), 6.69 (br t, J = 6 Hz, 1 H), 4.14 (dd, J = 7, 9 Hz, 1 H), 4.04 (m, 1 H), 3.46 (m, 2 H), 3.16-3.04 (m, 5 H), 2.87 (m, 1 H); 2.64 (dd, J = 4, 13 Hz, 1 H), 2.03 (m, 1 H), 1.75-1.63 (m, 5 H), 1.53 (m, 2 H), 1.39 (m, 1 H), 1.30 (d, J = 7 Hz, 3 H), 1.0-0.83 (m, 21 H), 0.74 (br t, J = 7 Hz, 3 H). HRMS (ESI) calcd for C₃₂H₅₅N₅O₄+H₁ 574.4332, found 574.4332.

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EXAMPLE 4. Preparation of N²-[(2S)-3-(3,5-difluorophenyl)-2-(3-[(dipropylamino)carbonyl]-5-methylbenzoyl)amino)propyl]-N¹-isobutyl-L-alaninamide hydrochloride



Preparation of N²-(tert-butoxycarbonyl)-N¹-isobutyl-L-alaninamide

N-tert-Butoxycarbonylalanine (2.8 g, 15 mmol) and carbonyldiimidazole (2.75 g, 17 mmol) are stirred together in 30 mL of dry THF under nitrogen for 1 h. To this is added 3 mL (30 mmol) of isobutyl amine, and the mixture is stirred for one week. It is then concentrated, dissolved in ethyl acetate, and washed successively with 1 N KHSO₄, water, and brine, and dries over Na₂SO₄. Concentration affords the title compound as a white solid (2.25 g, 9.2 mmol, 62%). ¹H NMR (CDCl₃) δ 6.27 (m, 1 H), 5.02 (m, 1 H), 4.13 (m, 1 H), 3.08 (m, 2 H), 1.77 (m, 1 H), 1.45 (s, 9 H), 1.35 (d, J = 7 Hz, 3 H), 0.90 (d, J = 7 Hz, 6 H).

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Preparation of N¹-isobutyl-L-alaninamide

N²-(tert-Butoxycarbonyl)-N¹-isobutyl-L-alaninamide (300 mg, 1.23 mmol) is stirred with 2 mL of TFA in 4 mL of dichloromethane for 1 h. The mixture is concentrated and neutralized with 2 mL of 1 N NaHCO₃ and 2 mL of 1 N Na₂CO₃, and extracted into 50 mL of ethyl ether containing 2 mL of methanol. The organic phase was washed with brine and dried with Na₂SO₄. Concentration afforded the title compound as a colorless film (90 mg, 0.62 mmol, 51%). ¹H NMR (CD₃OD) δ 4.9 (s, 3 H, includes water), 3.52 (q, J = 7 Hz, 1 H), 3.07-2.96 (m, 2 H), 1.78 (m, 1 H), 1.31 (d, J = 7 Hz, 3 H), 0.90 (m, 6 H).

Preparation of N²-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl) propyl]-N¹-isobutyl-L-alaninamide hydrochloride

N-t-butoxycarbonyl(3,5-difluorophenyl)alanal (EXAMPLE 2, 5 300 mg, 1.05 mmol) and N¹-isobutyl-L-alaninamide (170 mg, 1.18 mmol) are combined in 10 mL of dry THF under nitrogen. Sodium triacetoxycyanoborohydride (320 mg, 1.5 mmol) is added, followed by 5 mL of methanol. The mixture is stirred 4 days, concentrated, and dissolved in ethyl acetate and 5 mL of 10 methanol. The organic phase is washed with 1 N NaHCO₃ and with brine, dried over Na₂SO₄, and concentrated. The residue is dissolved in ethyl ether and acidified with ethereal HCl. The resulting solid is dissolved in a small amount of methanol and precipitated with ethyl ether, affording the title compound as 15 a tan solid (205 mg, 0.46 mmol, 43%). ¹H NMR (CD₃OD) δ 8.4 (m, 1 H), 6.77 (m, 2 H), 6.69 (m, 1 H), 3.99 (m, 2 H), 3.19 (t, J = 12 Hz, 1 H), 3.06 (m, 3 H), 2.88 (dd, 1 H), 2.77 (d, J = 7 Hz, 2 H), 1.77 (m, 1 H), 1.52 (d, J = 7 Hz, 3 H), 1.37 (s, 9 H), 0.92 (m, 6 H).

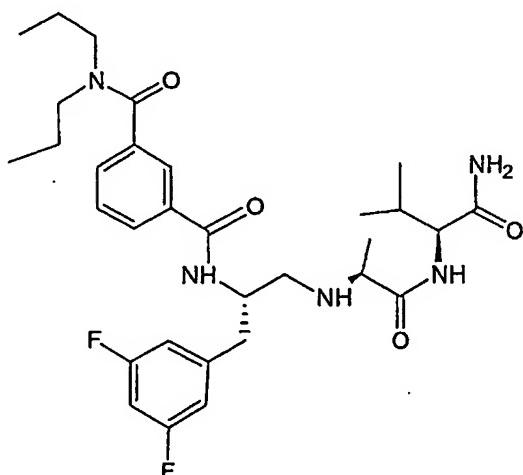
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Preparation of N²-[(2S)-3-(3,5-difluorophenyl)-2-{3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino]propyl]-N¹-isobutyl-L-alaninamide hydrochloride

N²-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5- 25 difluorophenyl) propyl]-N¹-isobutyl-L-alaninamide hydrochloride (238 mg, 0.53 mmol) is stirred with 2 mL of TFA and 3 mL of dichloromethane for 1 h. The mixture is concentrated, neutralized with 3 mL of 1 N NaHCO₃, and extracted into ethyl acetate containing 2% methanol. The organic phase is washed 30 with brine, dried over Na₂SO₄, and concentrated to a yellow oil (400 mg) which includes TFA. The residue is dissolved in 2 mL of DMF. To 1 mL of the resulting solution is added a solution of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid, (80 mg, 0.3 mmol), EDC (58 mg, 0.3 mmol) and HOBT (40 mg, 0.3 mmol) in 35 3 mL of DMF which has been stirred together under nitrogen for 1 h. The combined mixture is stirred for 5 days, and is then

quenched with 20 mL of water and dissolved in 120 mL of ethyl acetate containing 5 mL of methanol. The organic phase is washed with water, 1 N NaHCO₃, and brine, and dried over Na₂SO₄. It is concentrated and chromatographed over silica gel, eluting with 3% to 5 % methanol in chloroform to afford the free base of the title compound as a sticky solid (65 mg, 0.12 mmol, 45%). To a portion of this material is added ether and ethereal HCl, affording the title compound as an off-white solid. MS (CI) m/z 559 (MH⁺). HRMS (ESI) calcd for C₃₁H₄₄F₂N₄O₃+H₁ 559.3459, found 559.3455

EXAMPLE 5. Preparation of N-[(2S)-3-(3,5-difluorophenyl)-2-({3-[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-L-valinamide



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Preparation of N-(tert-butoxycarbonyl)-L-alanyl-L-valinamide

N-tert-Butoxycalanine (0.95 g, 5.0 mmol), EDC (1.0 g, 5.2 mmol), and HOBT (0.70 g, 5.2 mmol) are stirred in 10 mL of dry DMF under nitrogen for 1 h. N-Methylmorpholine (1.6 mL, 14.5 mmol) is added to L-valinamide hydrochloride (0.76 g, 5.0 mmol) in 7 mL of DMF, and the resulting suspension is agitated for 5-10 min and then added to the EDC mixture. The reaction mixture is stirred for 3 days. It is quenched with 1 N KHSO₄ and extracted into ethyl acetate. The organic phase is washed

successively with 1 N KHSO₄, 1N NaHCO₃, water, and brine, and dried with Na₂SO₄. Concentration and trituration with pentane affords the title compound as a white solid (1.07 g, 3.7 mmol, 74%). MS (CI) m/z 288 (MH⁺). HRMS (ESI) calcd for C₁₃H₂₅N₃O₄+H₁ 288.1923, found 288.1922.

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Preparation of L-alanyl-L-valinamide

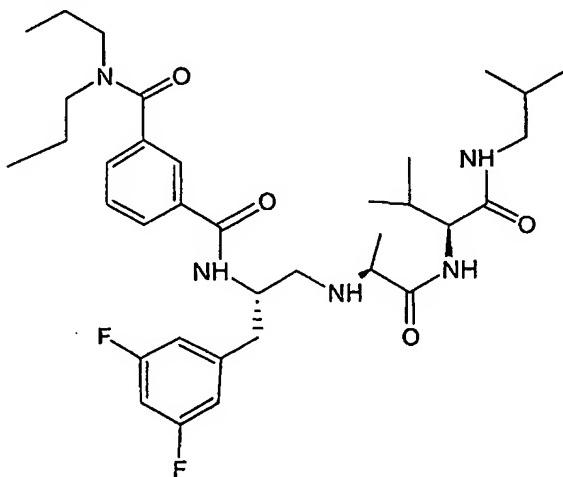
N-(tert-butoxycarbonyl)-L-alanyl-L-valinamide (0.5 g, 1.74 mmol) is stirred with 3 mL of TFA in 6 mL of dichloromethane 10 for 1 h. It is then concentrated, neutralized with 3.5 mL of 1N NaHCO₃ and 3.5 mL of 1N Na₂CO₃, and extracted into 60 mL of ethyl ether containing several mL of methanol. The aqueous phase is extracted with 100 mL of dichloromethane and 10 mL of methanol. The aqueous layer is evaporated and the solids are 15 extracted with methanol. This is concentrated to 180 mg (0.96 mmol, 55%) of an 85:15 mixture of the title compound and a minor diastereomer. The combined organic phases are concentrated to afford 74 mg (0.4 mmol, 23%) of the title compound as a white solid. HRMS (ESI) calcd for C₈H₁₇N₃O₂+H₁ 20 188.1399, found 188.1408..

Preparation of N-[(2S)-3-(3,5-difluorophenyl)-2-({3-[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-L-valinamide

25 N-t-butoxycarbonyl(3,5-difluorophenyl)alanal (EXAMPLE 2, 265 mg, 0.91 mmol) and L-alanyl-L-valinamide (180 mg, 0.96 mmol) are combined in 10 mL of dry THF under nitrogen. Sodium triacetoxycyanoborohydride (300 mg, 1.4 mmol) is added, followed by 3 mL of methanol. The mixture is stirred 3 days, 30 concentrated, and dissolved in ethyl acetate and 5 mL of methanol. The organic phase is washed with 1 N NaHCO₃, water, and brine, dried over Na₂SO₄, and concentrated. The residue, 275 mg, is dissolved in ethyl ether and ethereal HCl is added. The mother liquor is removed, and the residue is washed with ether 35 to afford 70 mg of a waxy solid. This solid is stirred with 1 mL of TFA and 2 mL of dichloromethane for 1 h. It is concentrated,

neutralized with several mL of 1 N NaHCO₃, and extracted into ethyl acetate containing several mL of methanol. The organic phase is washed with brine and dried over Na₂SO₄, and concentrated to 100 mg of a film, which includes TFA. This is dissolved in 1 mL of dry DMF and combined with a solution of 3-[(dipropylamino)carbonyl]benzoic acid, (38 mg, 0.15 mmol), EDC (29 mg, 0.15 mmol) and HOBT (20 mg, 0.15 mmol) in 2 mL of DMF which had been previously stirred together for 2 h. The resulting mixture is stirred under nitrogen for 6 days. It is quenched with water and 1 N KH₂PO₄ and extracted into a large volume of ethyl acetate containing 7% methanol. The organic phase is washed with 1 N NaHCO₃ and brine, dried over Na₂SO₄, and concentrated. Chromatography on silica gel, eluting with 5% to 7 % methanol in dichloromethane affords, after addition of ethereal HCl to the product-containing fractions and concentration, the title compound as a tan, friable glass (15 mg, 0.025 mmol, 18%). HRMS (ESI) calcd for C₃₁H₄₃F₂N₅O₄+H₁ 588.3361, found 588.3364

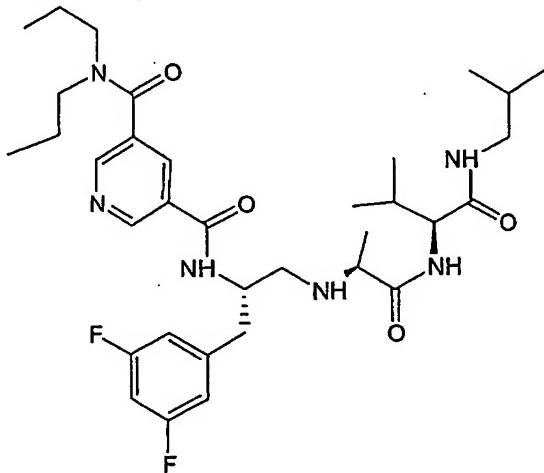
EXAMPLE 6. Preparation of N-[(2S)-3-(3,5-difluorophenyl)-2-({3-[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-N¹-isobutyl-L-valinamide



Following essentially the procedures described for EXAMPLE 2, but employing 3-[(dipropylamino)carbonyl]-benzoic acid in place of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid, is

obtained N-[(2S)-3-(3,5-difluorophenyl)-2-({3-
[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-N¹-
isobutyl-L-
valinamide. HRMS (ESI) calcd for C₃₅H₅₁F₂N₅O₄+H₁ 644.3987, found
5 644.3997.

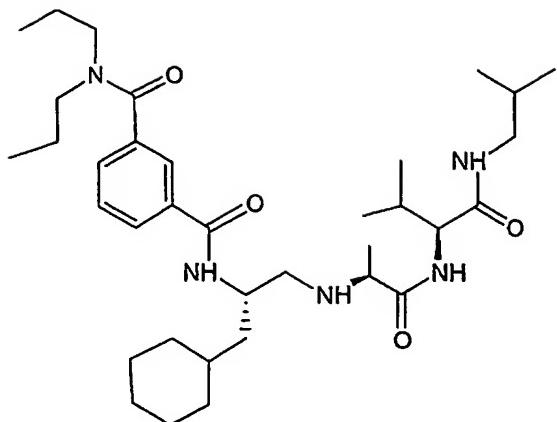
**EXAMPLE 7. Preparation of N-[(2S)-3-(3,5-difluorophenyl)-
2-[(5-[(dipropylamino)carbonyl]pyridin-3-
yl]carbonyl]amino)propyl]-L-alanyl-N¹-isobutyl-L-valinamide**



10

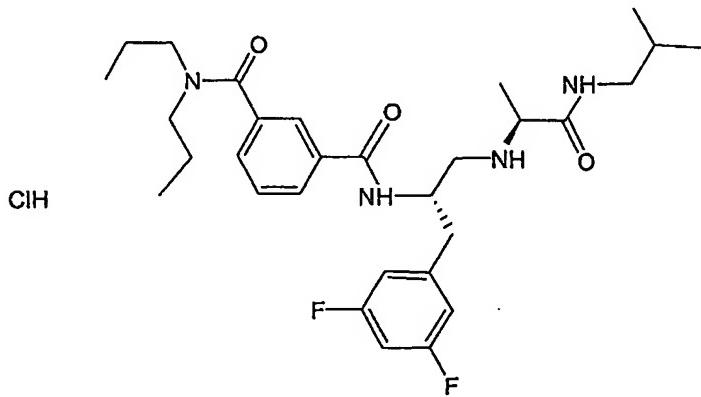
Following essentially the procedures described for EXAMPLE 2, but employing 5-[(dipropylamino)carbonyl]-nicotinic acid in place of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid, is
15 obtained N-[(2S)-3-(3,5-difluorophenyl)-2-[(5-
[(dipropylamino)carbonyl]pyridin-3-yl]carbonyl]amino)propyl]-L-
alanyl-N¹-isobutyl-L-valinamide. HRMS (ESI) calcd for
C₃₄H₅₀F₂N₆O₄+H₁ 645.3939, found 645.3939.

20 **EXAMPLE 8. Preparation of N-[(2S)-3-cyclohexyl-2-({3-
[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-N¹-
isobutyl-L-valinamide**



Following essentially the procedures described for **EXAMPLE 1**, but employing N-t-butoxycarbonylcyclo-hexylalanine methyl ester in place of N-t-butoxycarbonyl phenylalanine methyl ester, is obtained N-[{(2S)-3-cyclohexyl-2-[(3-[(dipropylamino)carbonyl]benzoyl]amino)propyl]-L-alanyl-N'-isobutyl-L-valinamide. HRMS (ESI) calcd for C₃₅H₅₉N₅O₄+H₁ 614.4645, found 614.4633

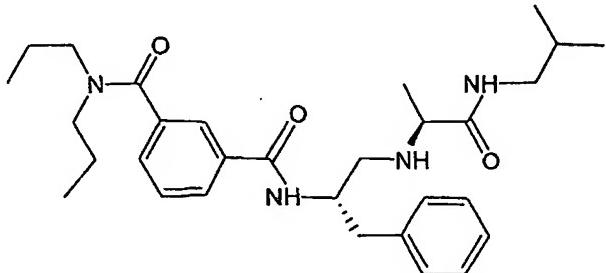
EXAMPLE 9. Preparation of N²-[(2S)-3-(3,5-difluorophenyl)-2-[(3-[(dipropylamino)carbonyl]benzoyl)amino)propyl]-N¹-isobutyl-L-alaninamide hydrochloride



Following essentially the procedures described for **EXAMPLE 4**, but employing 3-[(dipropylamino)carbonyl]-benzoic acid in place of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid, is obtained N²-[(2S)-3-(3,5-difluorophenyl)-2-[(3-[(dipropylamino)carbonyl]benzoyl)amino)propyl]-N¹-isobutyl-L-

alaninamide hydrochloride. MS (CI) m/z 545 (MH⁺). HRMS (ESI) calcd for C₃₀H₄₂F₂N₄O₃+H₁ 545.3303, found 545.3292.

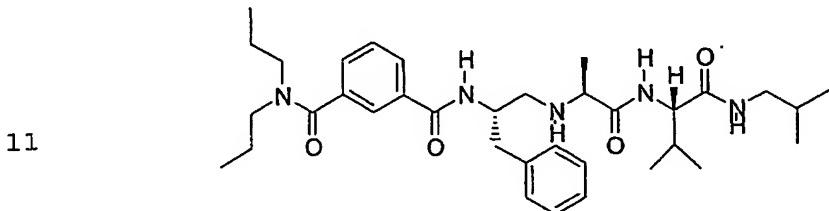
EXAMPLE 10. Preparation of N²-[(2S)-2-(3-[(dipropylamino)carbonyl]benzoyl)amino]-3-phenylpropyl]-N¹-isobutyl-L-alaninamide



Following essentially the procedures described for EXAMPLE 4, but employing 3-[(dipropylamino)carbonyl]-benzoic acid in place of 3-[(dipropylamino)carbonyl]-5-methylbenzoic acid, and employing N-t-butoxycarbonyl phenylalanine methyl ester in place of N-t-butoxycarbonyl(3,5-difluorophenyl)alanine methyl ester, and without HCl salt formation, is obtained N²-[(2S)-2-(3-[(dipropylamino)carbonyl]benzoyl)amino]-3-phenylpropyl]-N¹-isobutyl-L-alaninamide. MS (CI) m/z 509 (MH⁺) HRMS (ESI) calcd for C₃₀H₄₄N₄O₃+H₁ 509.3491, found 509.3488

Compounds of the invention include the following which are prepared essentially according to the procedures described in the charts, schemes, examples and preparations set forth herein.

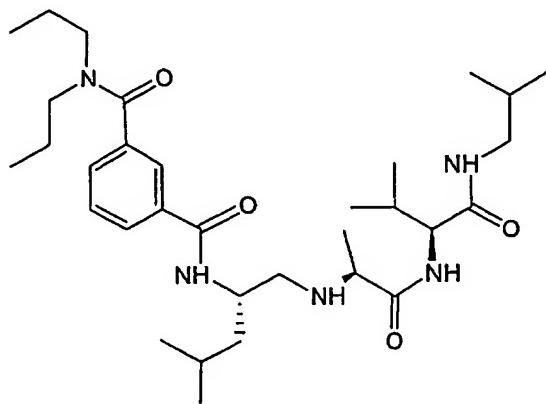
Example Structure/Name



N-[(2S)-2-(3-

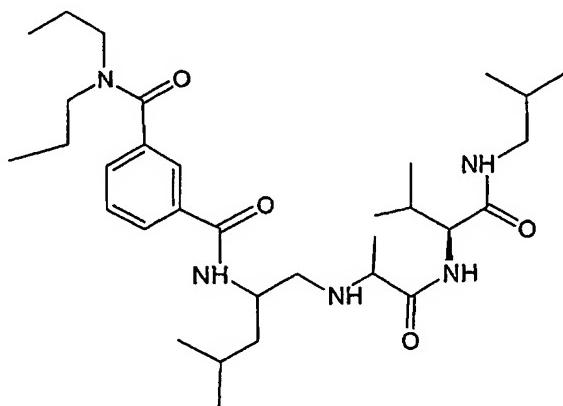
[(dipropylamino) carbonyl]benzoyl}amino) -3-
phenylpropyl] -L-alanyl-N¹-isobutyl-L-valinamide

12



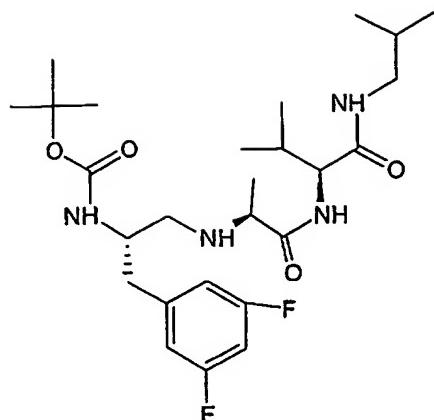
N- [(2*S*) -2 - ({3 -
[(dipropylamino) carbonyl]benzoyl}amino) -4 -
methylpentyl] -L-alanyl-*N*¹-isobutyl-L-valinamide

13



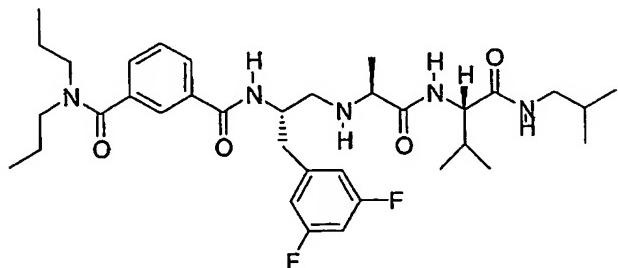
N- [2 - ({3 -
[(dipropylamino) carbonyl]benzoyl}amino) -4 -
methylpentyl] alanyl-*N*¹-isobutyl-L-valinamide

14



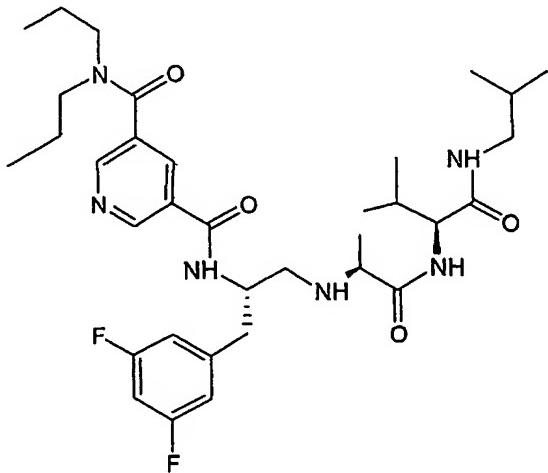
N-[(2*S*)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-difluorophenyl)propyl]-L-alanyl-*N*¹-isobutyl-L-valinamide

15



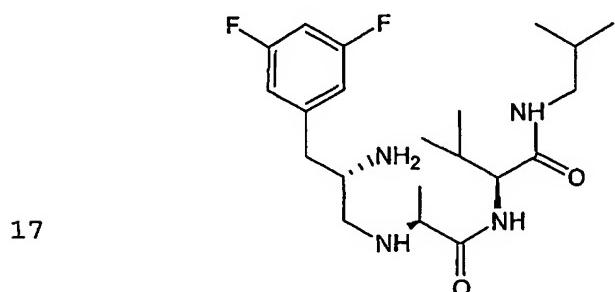
N-[(2*S*)-3-(3,5-difluorophenyl)-2-({(dipropylamino)carbonyl}benzoyl)amino]propyl-L-alanyl-*N*¹-isobutyl-L-valinamide

16

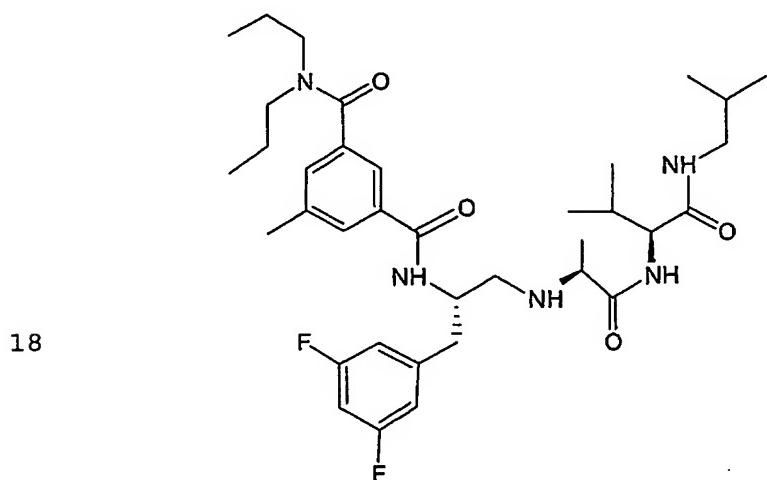


N-{(2*S*)-3-(3,5-difluorophenyl)-2-[{(5-

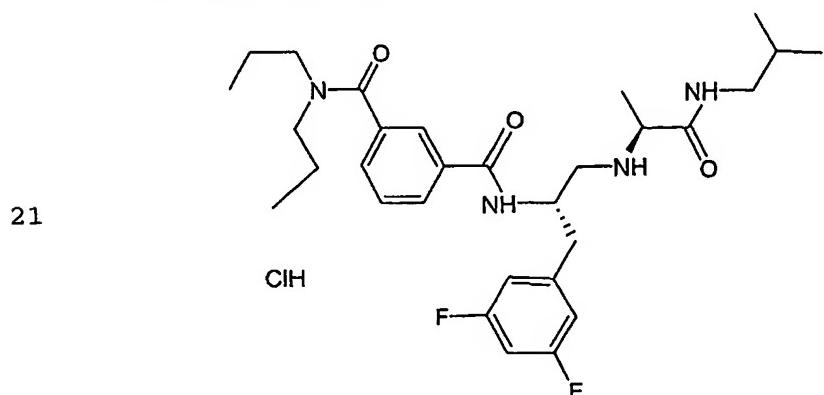
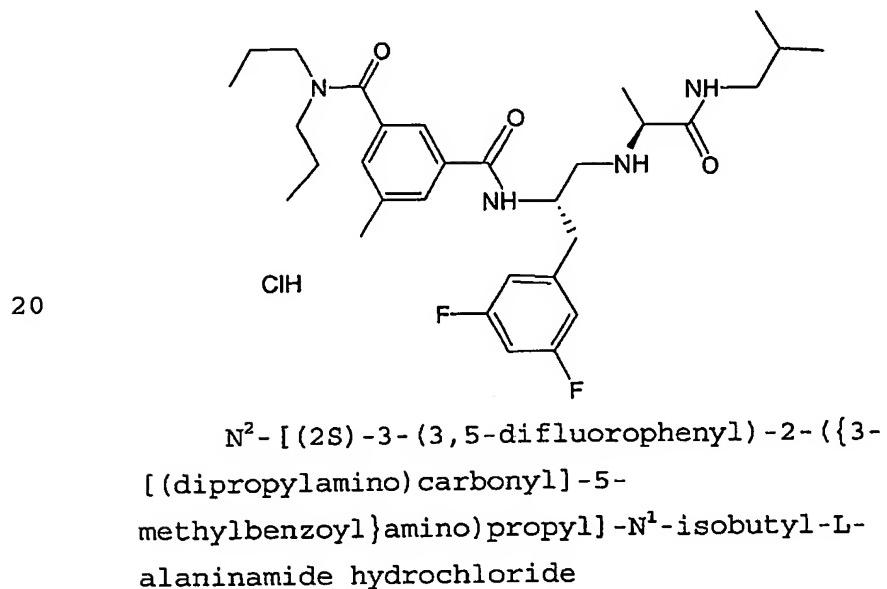
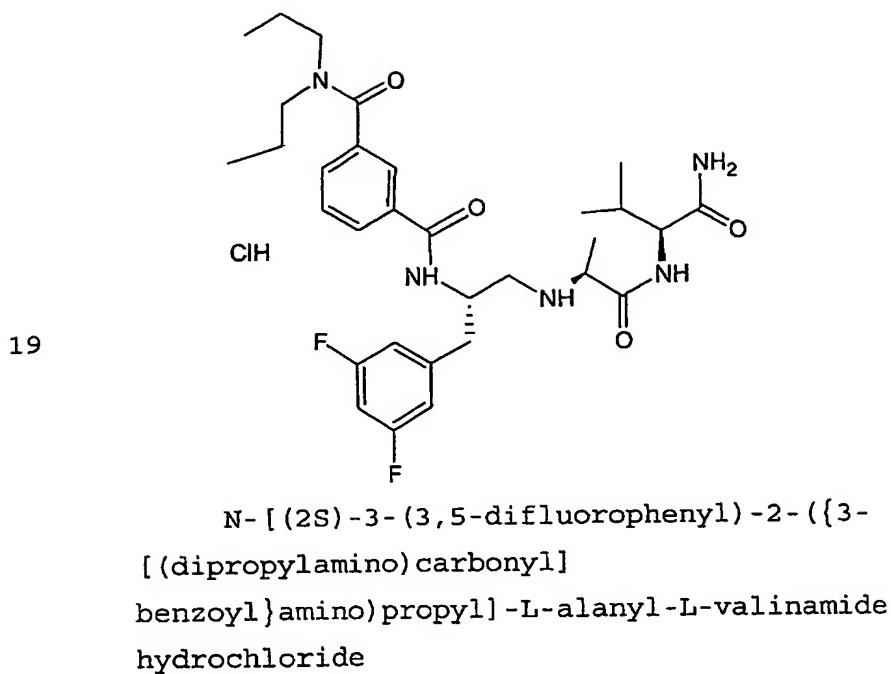
[(dipropylamino)carbonyl]pyridin-3-yl}carbonyl)amino]propyl}-L-alanyl-N¹-isobutyl-L-valinamide



N-[(2S)-2-amino-3-(3,5-difluorophenyl)propyl]-L-alanyl-N¹-isobutyl-L-valinamide

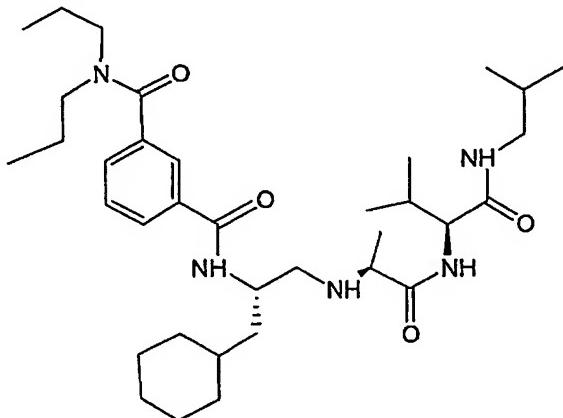


N-[(2S)-3-(3,5-difluorophenyl)-2-({3-[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)propyl]-L-alanyl-N¹-isobutyl-L-valinamide



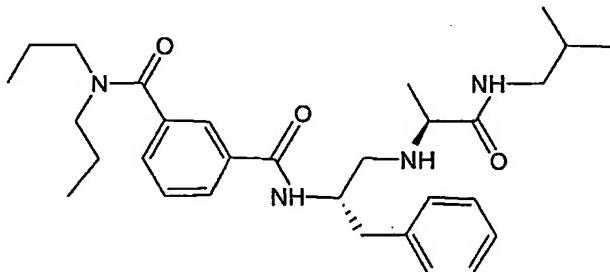
N^2 -[(2S)-3-[(3,5-difluorophenyl)-2-(3-[(dipropylamino)carbonyl]benzoyl)amino]propyl]-N¹-isobutyl-L-alaninamide hydrochloride

22



N -[(2S)-3-cyclohexyl-2-[(3-[(dipropylamino)carbonyl]benzoyl)amino]propyl]-L-alanyl-N¹-isobutyl-L-valinamide

23



N^2 -[(2S)-2-[(3-[(dipropylamino)carbonyl]benzoyl)amino]-3-phenylpropyl]-N¹-isobutyl-L-alaninamide

BIOLOGY EXAMPLES

5

Example A

Enzyme Inhibition Assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model APP substrate, MBP-C125SW, by the compounds assayed as compared

with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

25

Specific Assay Procedure:

Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc

diluted compound plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 5 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaOAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37 degrees C starts the enzyme 10 reaction. After 90 minutes at 37 degrees C, 200 microliters/well cold specimen diluent is added to stop the reaction and 20 microliters/well was transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction 15 is incubated overnight at 4 degrees C and the ELISA is developed the next day after a 2 hour incubation with anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.

Relative compound inhibition potency is determined by 20 calculating the concentration of compound that showed a fifty percent reduction in detected signal (IC_{50}) compared to the enzyme reaction signal in the control wells with no added compound. In this assay, preferred compounds of the invention exhibit an IC_{50} of less than 50 micromolar.

25

Example B

Cell Free Inhibition Assay Utilizing a Synthetic APP

Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by 30 the covalent attachment of Oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

35

Biotin-SEVNL-DAEFRC [oregon green] KK [SEQ ID NO:
1]
Biotin-SEVKM-DAEFRC [oregon green] KK [SEQ ID NO:
2]
5 Biotin-GLNIKTEEISEISY-EVEFRC [oregon green] KK [SEQ ID NO:
3]
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNL-DAEFRC [oregon green] KK
[SEQ ID NO:4]
Biotin-FVNQHLCoxGSHLVEALY-LVCoxGERGFFYTPKAC [oregon
10 green] KK [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acquirest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate. In this assay, preferred compounds of the invention exhibit an IC₅₀ of less than 50 micromolar.

Example C

Beta-Secretase Inhibition: P26-P4' SW Assay

35 Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity,

using the methods described, for example, in published PCT application WO00/47618. The P26-P4' SW substrate is a peptide of the sequence:

(biotin) CGGADRGLTTRPGSGLTNKTEEISEVNLDASF [SEQ ID NO: 6]

5 The P26-P1 standard has the sequence:

(biotin) CGGADRGLTTRPGSGLTNKTEEISEVNL [SEQ ID NO: 7].

Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a 10 substrate concentration of about 1.0 micromolar is preferred. Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give 15 product concentrations with the linear range of the ELISA assay, about 125 to 2000 picomolar, after dilution.

The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in 20 assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51 millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

25 Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the 30 samples are incubated with streptavidin-AP according to the manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with 35 streptavidin-alkaline phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-

secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

Example D

Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and detection methods are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

By way of example, one such peptide has the sequence SEVNL-DAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the sequence ADRGLTTRPGSGLTNIKTEEISEVNL-DAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the compound inhibitor to control results provides a measure of the compound's inhibitory activity.

Example E

Inhibition of Beta-Secretase Activity - Cellular Assay

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta

(Citron et al., 1992, *Nature* 360:672-674), as described in U.S. Patent No. 5,604,102.

The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired 5 concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors 10 to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

Example F

15 **Inhibition of Beta-Secretase in Animal Models of AD**

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, 20 transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

25 PDAPP mice, prepared as described in Games et al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of A beta release in the presence of putative inhibitory compounds. As described in U.S. Patent No. 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, 30 such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the 35 chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound.

Administration can be acute, i.e., single dose or multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and

5 analyzed for the presence of APP cleavage peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A beta and/or beta-amyloid plaques. The tissue

10 is also analyzed for necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

15

Example G

Inhibition of A Beta Production in Human Patients

Patients suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A beta in the brain. AD patients are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

25 Patients administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated patients.

Example H

Prevention of A Beta Production in Patients at Risk for AD

35 Patients predisposed or at risk for developing AD are identified either by recognition of a familial inheritance

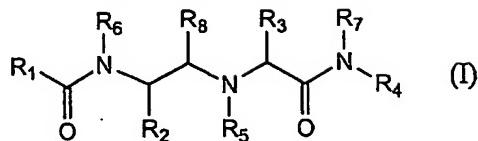
pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Patients identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier
5 suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Patients administered the compound inhibitors are expected
10 to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control,
15 non-treated patients.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may
20 be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of the formula I:



5 or a pharmaceutically acceptable salt thereof, wherein
 R₁ is H, R'₁₀₀, -(CRR')₁₋₆R'₁₀₀, -(CRR')₁₋₆-O-R'₁₀₀, -(CRR')₁₋₆-S-
 R'₁₀₀, -(CRR')₁₋₆-C(=O)-R₁₀₀, -(CRR')₁₋₆-SO₂-R₁₀₀ OR
 (CRR')₁₋₆-NR₁₀₀-R'₁₀₀;

10 R and R' independently are hydrogen, C₁-C₁₀ alkyl, C₁-C₁₀
 alkylaryl or C₁-C₁₀ alkylheteroaryl;

15 R₁₀₀ and R'₁₀₀ independently represent aryl,
 heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl,
 -aryl-W-heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-
 heteroaryl, -heteroaryl-W- heterocyclyl, -heterocyclyl-W-
 aryl, -heterocyclyl-W-heteroaryl, -heterocyclyl-W-
 heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-
 O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-
 heteroaryl, where the ring portions of each are optionally
 substituted with 1, 2, or 3 groups independently selected
 from

20 -OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -CF₃, -(CH₂)₀₋
 -₄O-P(=O)(OR')(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-
 (CH₂)₀₋₄-CONR₁₀₂R'₁₀₂, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋
 -₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl),
 -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -
 (CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-
 CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-
 O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈
 alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋
 -₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋
 -₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -
 (CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-
 R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-
 R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -

(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R_{150'}-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, and (C₂-C₁₀) alkynyl, or

R₁₀₀ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is -(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl) or -(C₁-C₆ alkyl)-S-(C₁-C₆ alkyl), each of which is optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is -O-(CH₂)_{n8}-R₄₋₅ where n₈ is 0 thru 2 and R₄₋₅ is C₁-C₆ alkyl or aryl, or

R₁₀₀ is C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups;

W is -(CH₂)₀₋₄-, -O-, -S(O)₀₋₂-, -N(R₁₃₅)-, -CR(OH)- or -C(O)-;

R₁₀₂ and R_{102'} independently are hydrogen, or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups that are independently halogen, aryl or -R₁₁₀;

R₁₀₅ and R'₁₀₅ independently represent -H, -R₁₁₀, -R₁₂₀, C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, or C₁-C₆ alkyl chain with one double bond and one triple bond, or C₁-C₆ alkyl optionally substituted with -OH or -NH₂; or, C₁-C₆ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, or

R₁₀₅ and R'₁₀₅ together with the atom to which they are attached form a 3 to 7 membered carbocyclic ring, where one member is optionally a heteratom selected from -O-, -S(O)₀₋₂-, -N(R₁₃₅)-, the ring being optionally substituted with 1, 2 or 3 independently selected R₁₄₀ groups;

R₁₁₅ at each occurrence is independently halogen, -OH, -CO₂R₁₀₂, -C₁-C₆ thioalkoxy, -CO₂-phenyl, -NR₁₀₅R'₁₃₅, -SO₂-(C₁-C₈ alkyl), -C(=O)R₁₈₀, R₁₈₀, -CONR₁₀₅R'₁₀₅, -SO₂NR₁₀₅R'₁₀₅, -NH-CO-(C₁-C₆ alkyl), -NH-C(=O)-OH, -NH-C(=O)-OR, -NH-C(=O)-O-phenyl, -O-C(=O)-(C₁-C₆ alkyl), -O-C(=O)-amino, -O-C(=O)-mono- or dialkylamino, -O-C(=O)-phenyl, -O-(C₁-C₆ alkyl)-CO₂H, -NH-SO₂-(C₁-C₆ alkyl), C₁-C₆ alkoxy or C₁-C₆ haloalkoxy;

R_{135} is C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, $-(CH_2)_{0-2-}(aryl)$, $-(CH_2)_{0-2-}(heteroaryl)$, or $-(CH_2)_{0-2-}(heterocyclyl)$;

R_{140} is heterocyclyl optionally substituted with 1, 2, 3, or 4 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, amino(C_1 - C_6)alkyl, mono(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, di(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, and =O;

R_{150} is hydrogen, C_3 - C_7 cycloalkyl, $-(C_1-C_2$ alkyl)-(C_3-C_7 cycloalkyl), C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkyl with one double bond and one triple bond, $-R_{110}$, $-R_{120}$, or C_1 - C_6 alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from -OH, -NH₂, C_1 - C_3 alkoxy, R_{110} , and halogen;

R_{150}' is C_3 - C_7 cycloalkyl, $-(C_1-C_3$ alkyl)-(C_3-C_7 cycloalkyl), C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkyl with one double bond and one triple bond, $-R_{110}$, $-R_{120}$, or C_1 - C_6 alkyl optionally substituted with 1, 2, 3, or 4 groups independently selected from -OH, -NH₂, C_1 - C_3 alkoxy, R_{110} , and halogen;

R_{180} is selected from morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S-oxide, homothiomorpholinyl S,S-dioxide, pyrrolinyl and pyrrolidinyl, each of which is optionally substituted with 1, 2, 3, or 4 groups independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, hydroxy, cyano, nitro, amino, mono(C_1 - C_6)alkylamino, di(C_1 - C_6)alkylamino, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, amino(C_1 - C_6)alkyl, mono(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, di(C_1 - C_6)alkylamino(C_1 - C_6)alkyl, and =O;

R_{110} is aryl optionally substituted with 1 or 2 R_{125} groups;

R_{125} at each occurrence is independently halogen, amino, mono- or dialkylamino, -OH, -C≡N, -SO₂-NH₂, -SO₂-NH- C_1 - C_6 alkyl, -

SO₂-N(C₁-C₆ alkyl)₂, -SO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH-C₁-C₆ alkyl, or -CO-N(C₁-C₆ alkyl)₂, or

5 C₁-C₆ alkyl, C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups that are independently selected from C₁-C₃ alkyl, halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- and dialkylamino, or

C₁-C₆ alkoxy optionally substituted with one, two or three of halogen;

10 R₁₂₀ is heteroaryl, which is optionally substituted with 1 or 2 R₁₂₅ groups; and

R₁₃₀ is heterocyclyl optionally substituted with 1 or 2 R₁₂₅ groups;

R₂ is .

15 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-

N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -

C₁-C₃ alkoxy, amino, mono- or dialkylamino, -

20 N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently

selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃

25 alkoxy, amino, and mono- or dialkylamino, or

- (CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is

optionally substituted with 1, 2, or 3 groups

independently selected from the group consisting of

R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆

30 alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or

aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆

alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where

the ring portions of each are optionally substituted

with 1, 2, 3, or 4 groups independently selected from

halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -

N(R)COR', -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino,

-SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino,
-C(=O)-monoalkylamino, -C(=O)-dialkylamino,
-SO₂-(C₁-C₄) alkyl,
C₁-C₆ alkoxy optionally substituted with 1, 2, or 3
5 groups which are independently selected from
halogen,
C₃-C₇ cycloalkyl optionally substituted with 1, 2, or
3 groups independently selected from halogen, -
OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆
10 alkyl and mono- or dialkylamino,
C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
groups independently selected from halogen, -OH,
-SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or
dialkylamino and -C₁-C₃ alkyl, and
15 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is
optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, -SH,
-C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and
mono- or dialkylamino; and the heterocyclyl
20 group is optionally further substituted with
oxo;
R₃ is H or is
C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, =O, -COOH,
25 -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-
N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃
alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -
OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or
30 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally
substituted with 1, 2, or 3 groups independently
selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃
alkoxy, amino, and mono- or dialkylamino, or
35 -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is
optionally substituted with 1, 2, or 3 groups
independently selected from the group consisting of

R_{205} , -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or
 5 aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino,
 10 -SO₂-(C₁-C₄) alkyl,
 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,
 15 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,
 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and
 20 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;
 25 R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heterocyclyl, -
 30 - 110 -

(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-aryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-(R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂, -CH(heterocyclyl)₂, -CH(aryl)(heteroaryl), -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl, -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C₁-C₄ alkyl), -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂, -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀), or

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -NR₂₃₅C=ONR₂₃₅R₂₄₀, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀, or -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocyclyl wherein one, two or three carbons of the cyclopentyl, cyclohexyl, or cycloheptyl is optionally replaced with a heteroatom independently selected from NH, NR₂₁₅, O, and S(=O)₀₋₂, and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group is optionally substituted with one or two groups that are independently R₂₀₅, =O, -CO-NR₂₃₅R₂₄₀, or -SO₂-(C₁-C₄ alkyl), or C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl, each of which is optionally substituted with 1, 2, or 3 independently selected R₂₀₅ groups, wherein each aryl and heteroaryl is optionally substituted with 1, 2, or 3 R₂₀₀, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, or 4 independently selected R₂₁₀; R₂₀₀ at each occurrence is independently selected from -OH, -NO₂, halogen, -CO₂H, C≡N, -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂

alkynyl), - (CH₂)₀₋₄-CO- (C₃-C₇ cycloalkyl), - (CH₂)₀₋₄-CO-aryl,
- (CH₂)₀₋₄-CO-heteroaryl, - (CH₂)₀₋₄-CO-heterocyclyl, - (CH₂)₀₋₄-
CO-O-R₂₁₅, - (CH₂)₀₋₄-SO₂-NR₂₂₀R₂₂₅, - (CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -
(CH₂)₀₋₄-SO₂- (C₁-C₁₂ alkyl), - (CH₂)₀₋₄-SO₂- (C₃-C₇ cycloalkyl),
5 - (CH₂)₀₋₄-N(H or R₂₁₅)-CO-O-R₂₁₅, - (CH₂)₀₋₄-N(H or R₂₁₅)-CO-
N(R₂₁₅)₂, - (CH₂)₀₋₄-N-CS-N(R₂₁₅)₂, - (CH₂)₀₋₄-N(-H or R₂₁₅)-CO-
R₂₂₀, - (CH₂)₀₋₄-NR₂₂₀R₂₂₅, - (CH₂)₀₋₄-O-CO- (C₁-C₆ alkyl), - (CH₂)₀₋
10 -₄O-P(O)-(OR₂₄₀)₂, - (CH₂)₀₋₄-O-CO-N(R₂₁₅)₂, - (CH₂)₀₋₄-O-CS-
N(R₂₁₅)₂, - (CH₂)₀₋₄-O-(R₂₁₅), - (CH₂)₀₋₄-O-(R₂₁₅)-COOH, - (CH₂)₀₋₄-
15 S-(R₂₁₅), - (CH₂)₀₋₄-O-(C₁-C₆ alkyl optionally substituted
with 1, 2, 3, or 5-F), C₃-C₇ cycloalkyl, - (CH₂)₀₋₄-N(H or
R₂₁₅)-SO₂-R₂₂₀, - (CH₂)₀₋₄-C₃-C₇ cycloalkyl,
C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
independently selected R₂₀₅ groups,

15 C₂-C₁₀ alkenyl and C₂-C₁₀ alkynyl, each of which is
optionally substituted with 1 or 2 independently
selected R₂₀₅ groups, wherein
the aryl and heteroaryl groups at each occurrence are
optionally substituted with 1, 2, or 3 groups that
20 are independently R₂₀₅, R₂₁₀, or
C₁-C₆ alkyl substituted with 1, 2, or 3 groups that
are independently R₂₀₅ or R₂₁₀, and wherein
the heterocyclyl group at each occurrence is optionally
substituted with 1, 2, or 3 groups that are
25 independently R₂₁₀;

R₂₀₅ at each occurrence is independently selected from C₁-C₆
alkyl, halogen, -OH, -O-phenyl, -SH, -S-C₁-C₆ alkyl, -C≡N,
-CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl) or N-(C₁-C₆
alkyl)(C₁-C₆ alkyl);

30 R₂₁₀ at each occurrence is independently selected from halogen,
C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -NR₂₂₀R₂₂₅, OH, C≡N, -CO-(C₁-
C₄ alkyl), -SO₂-NR₂₃₅R₂₄₀, -CO-NR₂₃₅R₂₄₀, -SO₂- (C₁-C₄ alkyl), =O,
or
C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₇
35 cycloalkyl, each of which is optionally substituted
with 1, 2, or 3 R₂₀₅ groups;

R₂₁₅ at each occurrence is independently selected from C₁-C₆ alkyl, -(CH₂)₀₋₂-(aryl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, and -(CH₂)₀₋₂-(heteroaryl), -(CH₂)₀₋₂-(heterocyclyl), wherein

5 the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀, and wherein the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 independently selected R₂₁₀;

10 R₂₂₀ and R₂₂₅ at each occurrence are independently selected from -H, -C₃-C₇ cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C₇ cycloalkyl), -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₁-C₆ alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, and -C₁-C₁₀ alkyl optionally substituted with -OH, -NH₂ or halogen, wherein

15 the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 independently selected R₂₇₀ groups

20 R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

25 R₂₄₅ and R₂₅₀ at each occurrence are independently selected from -H, C₁-C₄ alkyl, C₁-C₄ alkylaryl, C₁-C₄ alkylheteroaryl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, and phenyl; or

30 R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, -SO₂-, and -NR₂₂₀;

35 R₂₅₅ and R₂₆₀ at each occurrence are independently selected from -H, -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-aryl, -(C₁-C₄ alkyl)-heteroaryl, -(C₁-C₄ alkyl)-heterocyclyl, -aryl, -heteroaryl, -heterocyclyl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-aryl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heteroaryl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heterocyclyl, and

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from R₂₀₅, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), wherein 5 each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀, or C₁-C₆ alkyl substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, 10 or 4 R₂₁₀;

R₂₆₅ at each occurrence is independently -O-, -S- or -N(C₁-C₆ alkyl)-;

R₂₇₀ at each occurrence is independently R₂₀₅, halogen C₁-C₆ 15 alkoxy, C₁-C₆ haloalkoxy, NR₂₃₅R₂₄₀, -OH, -C≡N, -CO-(C₁-C₄ alkyl), -SO₂-NR₂₃₅R₂₄₀, -CO-NR₂₃₅R₂₄₀, -SO₂-(C₁-C₄ alkyl), =O, or C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or -(CH₂)₀₋₄-C₃-C₇ 20 cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R₂₀₅ groups;

R₅, R₆ and R₇, at each occurrence are independently H or -CO-O-(CH₂)_{n8}-R₄₋₅ where n₈ is 0 thru 2 and R₄₋₅ is C₁-C₆ 25 alkyl or phenyl; and

R₈ is H or C₁-C₆ alkyl optionally substituted with one, two or three substituents independently selected from the group consisting of C₁-C₃ alkyl, -F, -Cl, -Br, -I, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, -NR_{1-a}R_{1-b} where R_{1-a} and R_{1-b} are independently -H or C₁-C₆ alkyl.

2. A compound according to claim 1 wherein R₅, R₆, R₇, R₈, and R₉ are each hydrogen. 30

3. A compound according to claim 1 wherein R₂ is -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are 35 optionally substituted with 1, 2, 3, or 4 groups

independently selected from halogen, -OH, -SH, -C≡N,
-NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', or -N(R)SO₂R',
-C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-mono or
dialkylamino, -C(=O)-amino, -C(=O)-mono or
dialkylamino, -SO₂-(C₁-C₄) alkyl, or
C₁-C₆ alkoxy optionally substituted with 1, 2, or 3
groups which are independently selected from
halogen, or
C₃-C₇ cycloalkyl optionally substituted with 1, 2, or
10. 3 groups independently selected from halogen, -
OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆
alkyl and mono- or dialkylamino, or
C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3
groups independently selected from halogen, -OH,
15 -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or
dialkylamino and -C₁-C₃ alkyl, or
C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is
optionally substituted with 1, 2, or 3 groups
independently selected from halogen, -OH, -SH,
20 -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and
mono- or dialkylamino; and the heterocyclyl
group is optionally further substituted with
oxo; or
R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups
25 independently selected from halogen, -OH, =O, -SH,
-C≡N, -CF₃, -C₁-C₃ alkoxy, -S-(C₁-C₃)alkyl, amino,
mono- or dialkylamino, -N(R)C(O)R'-, -OC(=O)-amino
and -OC(=O)-mono- or dialkylamino, or
C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally
30 substituted with 1, 2, or 3 groups independently
selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃
alkoxy, amino, and mono- or dialkylamino.

4. A compound according to claim 1 wherein

35 R₁ is -(CRR')₀₋₆R₁₀₀;

R₁₀₀ represents aryl, heteroaryl, heterocyclyl, -aryl-W-aryl, -aryl-W-heteroaryl, -aryl-W-heterocyclyl, -heteroaryl-W-aryl, -heteroaryl-W-heteroaryl, -heteroaryl-W-heterocyclyl, -heterocyclyl-W-aryl, -heterocyclyl-W-heterocyclyl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-aryl, -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heterocyclyl or -CH[(CH₂)₀₋₂-O-R₁₅₀]-(CH₂)₀₋₂-heteroaryl, where the ring portions of each are optionally substituted with 1, 2, or 3 groups independently selected from

-OR, -NO₂, C₁-C₆ alkyl, halogen, -C≡N, -OCF₃, -(CH₂)₀₋₄-O-P(=O)(OR)(OR'), -(CH₂)₀₋₄-CO-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-O-(CH₂)₀₋₄-CONR₁₀₂R₁₀₂', -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(CH₂)₀₋₄(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-R₁₁₀, -(CH₂)₀₋₄-R₁₂₀, -(CH₂)₀₋₄-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₁₀, -(CH₂)₀₋₄-CO-R₁₂₀, -(CH₂)₀₋₄-CO-R₁₃₀, -(CH₂)₀₋₄-CO-R₁₄₀, -(CH₂)₀₋₄-CO-O-R₁₅₀, -(CH₂)₀₋₄-SO₂-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(CH₂)₀₋₄-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-N(R₁₅₀)-CO-O-R₁₅₀, -(CH₂)₀₋₄-N(R₁₅₀)-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-N(R₁₅₀)-CO-R₁₀₅, -(CH₂)₀₋₄-NR₁₀₅R'₁₀₅, -(CH₂)₀₋₄-R₁₄₀, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(O-R₁₁₀)₂, -(CH₂)₀₋₄-O-CO-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-CS-N(R₁₅₀)₂, -(CH₂)₀₋₄-O-(R₁₅₀), -(CH₂)₀₋₄-O-R₁₅₀'-COOH, -(CH₂)₀₋₄-S-(R₁₅₀), -(CH₂)₀₋₄-N(R₁₅₀)-SO₂-R₁₀₅, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, (C₂-C₁₀) alkenyl, or (C₂-C₁₀) alkynyl, or

R₁₀₀ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is -(C₁-C₆ alkyl)-O-C₁-C₆ alkyl) or -(C₁-C₆ alkyl)-S-(C₁-C₆ alkyl), each of which is optionally substituted with 1, 2, or 3 R₁₁₅ groups, or

R₁₀₀ is C₃-C₈ cycloalkyl optionally substituted with 1, 2, or 3 R₁₁₅ groups.

35 5. A compound according to claim 1 wherein
R₃ is H or is

5 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl) (C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or
10 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or
15 -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl) (C₁-C₆ alkyl).

6. A compound according to claim 1 wherein
20 R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-heterocyclyl,
25 heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-aryl-aryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-aryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heterocyclyl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-aryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-(R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂,
30 -CH(heterocyclyl)₂, -CH(aryl)(heteroaryl), -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl, -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C₁-C₄ alkyl), -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂, -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀), or
35 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -NR₂₃₅C=ONR₂₃₅R₂₄₀, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀, or

- $(CH_2)_{0-3}$ - (C_3-C_8) cycloalkyl wherein the cycloalkyl is
optionally substituted with 1, 2, or 3 groups
independently selected from the group consisting of
 R_{205} , $-CO_2H$, $-CO_2-(C_1-C_4$ alkyl), $-CO-NH_2$, $-CO-NH(C_1-C_6$
alkyl) and $-CO-N-(C_1-C_6$ alkyl) $(C_1-C_6$ alkyl).

5

7. A compound according to claim 1 selected from the group
consisting of:

N -[(2S)-2-({3-[dipropylamino]carbonyl}-
benzoyl)amino]-3-phenylpropyl-L-alanyl- N^1 -isobutyl-L-
valinamide,

N -[(2S)-3-(3,5-difluorophenyl)-2-({3-
[dipropylamino]carbonyl}-5-methylbenzoyl)amino]propyl-
L-alanyl- N^1 -isobutyl-L-valinamide,

N -[(2S)-2-({3-[dipropylamino]carbonyl}
benzoyl)amino]-4-methylpentyl-L-alanyl- N^1 -isobutyl-L-
valinamide,

N^2 -[(2S)-3-(3,5-difluorophenyl)-2-({3-
[dipropylamino]carbonyl}-5-methylbenzoyl)amino]propyl-
 N^1 -isobutyl-L-alaninamide hydrochloride,

N -[(2S)-3-(3,5-difluorophenyl)-2-({3-
[dipropylamino]carbonyl}benzoyl)amino]propyl-L-alanyl-
L-valinamide,

N -[(2S)-3-(3,5-difluorophenyl)-2-({3-
[dipropylamino]carbonyl}benzoyl)amino]propyl-L-alanyl-
 N^1 -isobutyl-L-valinamide,

N -{(2S)-3-(3,5-difluorophenyl)-2-[(5-
[dipropylamino]carbonyl)amino]propyl}-L-alanyl- N^1 -isobutyl-L-
valinamide,

N -[(2S)-3-cyclohexyl-2-({3-[dipropylamino]carbonyl}
benzoyl) amino]propyl-L-alanyl- N^1 -isobutyl-L-valinamide,

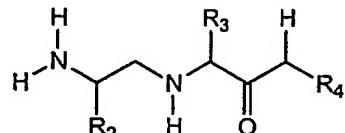
N^2 -[(2S)-3-(3,5-difluorophenyl)-2-({3-
[dipropylamino]carbonyl} benzoyl)amino]propyl]- N^1 -
isobutyl-L-alaninamide hydrochloride,

N^2 -[(2S)-2-({3-[dipropylamino]carbonyl}]

benzoyl}amino)-3-phenylpropyl]-N¹-isobutyl-L-alaninamide,
N-[(2S)-2-(3-[
[(dipropylamino)carbonyl]benzoyl}amino)-3-phenylpropyl]-
L-alanyl-N¹-isobutyl-L-valinamide,
N-[(2S)-2-(3-[
[(dipropylamino)carbonyl]benzoyl}amino)-4-methylpentyl]-
L-alanyl-N¹-isobutyl-L-valinamide,
N-[2-(3-[(dipropylamino)carbonyl]benzoyl}amino)-4-
methylpentyl]alanyl-N¹-isobutyl-L-valinamide,
N-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-(3,5-
difluorophenyl)propyl]-L-alanyl-N¹-isobutyl-L-valinamide,
N-[(2S)-3-(3,5-difluorophenyl)-2-(3-
[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-
N¹-isobutyl-L-valinamide,
N-[(2S)-3-(3,5-difluorophenyl)-2-[(5-
[(dipropylamino)carbonyl]pyridin-3-
yl)carbonyl]amino)propyl]-L-alanyl-N¹-isobutyl-L-
valinamide,
N-[(2S)-3-(3,5-difluorophenyl)-2-(3-
[(dipropylamino)carbonyl]-5-
methylbenzoyl}amino)propyl]-L-alanyl-N¹-isobutyl-L-
valinamide,
N-[(2S)-3-(3,5-difluorophenyl)-2-(3-
[(dipropylamino)carbonyl]benzoyl}amino)propyl]-L-alanyl-
L-valinamide hydrochloride,
N²-[(2S)-3-(3,5-difluorophenyl)-2-(3-
[(dipropylamino)carbonyl]-5-methylbenzoyl}amino)propyl]-
N¹-isobutyl-L-alaninamide hydrochloride,
N²-[(2S)-3-(3,5-difluorophenyl)-2-(3-
[(dipropylamino)carbonyl]benzoyl}amino)propyl]-N¹-
isobutyl-L-alaninamide hydrochloride,
N-[(2S)-3-cyclohexyl-2-(3-[(dipropylamino)carbonyl]
benzoyl}amino)propyl]-L-alanyl-N¹-isobutyl-L-valinamide,
and
N²-[(2S)-2-(3-[(dipropylamino)carbonyl]
benzoyl}amino)-3-phenylpropyl]-N¹-isobutyl-L-alaninamide.

8. A method for the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease comprising administration of a therapeutically effective amount of a compound or salt according to Claim 1, to a patient in need thereof.
- 15 9. A method of treatment as in claim 8, wherein the patient is a human.
- 10 10. A method of treatment according to claim 8, wherein the disease is dementia.
- 20 11. A method for making a compound of claim 1.

12. A compound of the formula V:



(V)

- 25 or a pharmaceutically acceptable salt thereof, wherein R₂ is C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -

N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

5 - (CH₂)₀₋₃- (C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂- (C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N- (C₁-C₆ alkyl) (C₁-C₆ alkyl), or

10 aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -

15 N(R)COR', -N(R)SO₂R', -C(=O)- (C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino,

20 -SO₂- (C₁-C₄) alkyl,

C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,

25 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -

OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,

30 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and

35 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl

group is optionally further substituted with oxo;

R₃ is H or is

C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, =O, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), -SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino, -N(R)C(O)R', -OC(=O)-amino and -OC(=O)-mono- or dialkylamino, or

5 C₂-C₆ alkenyl or C₂-C₆ alkynyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, and mono- or dialkylamino, or

10 - (CH₂)₀₋₃- (C₃-C₈) cycloalkyl wherein the cycloalkyl is optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or

15 aryl, heteroaryl, heterocyclyl, -C₁-C₆ alkyl-aryl, -C₁-C₆ alkyl-heteroaryl, or -C₁-C₆ alkyl-heterocyclyl, where the ring portions of each are optionally substituted with 1, 2, 3, or 4 groups independently selected from halogen, -OH, -SH, -C≡N, -NO₂, -NR₁₀₅R'₁₀₅, -CO₂R, -N(R)COR', -N(R)SO₂R', -C(=O)-(C₁-C₄) alkyl, -SO₂-amino, -SO₂-monoalkylamino, -SO₂-dialkylamino, -C(=O)-amino, -C(=O)-monoalkylamino, -C(=O)-dialkylamino, -SO₂-(C₁-C₄) alkyl,

20 C₁-C₆ alkoxy optionally substituted with 1, 2, or 3 groups which are independently selected from halogen,

25 C₃-C₇ cycloalkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, -C₁-C₆ alkyl and mono- or dialkylamino,

30 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH,

35 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH,

-SH, -C≡N, -CF₃, -C₁-C₃ alkoxy, amino, mono- or dialkylamino and -C₁-C₃ alkyl, and
 5 C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl each of which is optionally substituted with 1, 2, or 3 groups independently selected from halogen, -OH, -SH, -C≡N, -CF₃, C₁-C₃ alkoxy, amino, C₁-C₆ alkyl and mono- or dialkylamino; and the heterocyclyl group is optionally further substituted with oxo;

10 R₄ is hydrogen, -(CR₂₄₅R₂₅₀)₀₋₄-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-arylheterocyclyl,
 15 -(CR₂₄₅R₂₅₀)₀₋₄-aryl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-aryl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heterocyclyl, -(CR₂₄₅R₂₅₀)₀₋₄-heteroaryl-heteroaryl, -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-heteroaryl,
 20 -(CR₂₄₅R₂₅₀)₀₋₄-heterocyclyl-aryl, -[C(R₂₅₅)(R₂₆₀)]₁₋₃-CO-N-(R₂₅₅)₂, -CH(aryl)₂, -CH(heteroaryl)₂,
 25 -CH(heterocyclyl)₂, -CH(aryl)(heteroaryl), -(CH₂)₀₋₁CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-aryl, -(CH₂)₀₋₁-CH((CH₂)₀₋₆-OH)-(CH₂)₀₋₁-heteroaryl, -CH(-aryl or -heteroaryl)-CO-O(C₁-C₄ alkyl), -CH(-CH₂-OH)-CH(OH)-phenyl-NO₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl)-OH; -CH₂-NH-CH₂-CH(-O-CH₂-CH₃)₂, -(CH₂)₀₋₆-C(=NR₂₃₅)(NR₂₃₅R₂₄₀), or
 30 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -OC=ONR₂₃₅R₂₄₀, -S(=O)₀₋₂(C₁-C₆ alkyl), -SH, -NR₂₃₅C=ONR₂₃₅R₂₄₀, -C=ONR₂₃₅R₂₄₀, and -S(=O)₂NR₂₃₅R₂₄₀, or -(CH₂)₀₋₃-(C₃-C₈) cycloalkyl wherein the cycloalkyl is
 35 optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of R₂₀₅, -CO₂H, -CO₂-(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl) and -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), or cyclopentyl, cyclohexyl, or cycloheptyl ring fused to aryl, heteroaryl, or heterocyclyl wherein one, two or three carbons of the cyclopentyl, cyclohexyl, or

cycloheptyl is optionally replaced with a heteroatom independently selected from NH, NR₂₁₅, O, and S(=O)₀₋₂, and wherein the cyclopentyl, cyclohexyl, or cycloheptyl group is optionally substituted with one or two groups that are independently R₂₀₅, =O, -CO-NR₂₃₅R₂₄₀, or -SO₂-(C₁-C₄ alkyl), or C₂-C₁₀ alkenyl or C₂-C₁₀ alkynyl, each of which is optionally substituted with 1, 2, or 3 independently selected R₂₀₅ groups, wherein

5 each aryl and heteroaryl is optionally substituted with 1, 2, or 3 R₂₀₀, and wherein each heterocyclyl is optionally substituted with 1, 2, 3, or 4 independently selected R₂₁₀;

10 R₂₀₀ at each occurrence is independently selected from -OH, -NO₂, halogen, -CO₂H, C≡N, -(CH₂)₀₋₄-CO-NR₂₂₀R₂₂₅, -(CH₂)₀₋₄-CO-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkenyl), -(CH₂)₀₋₄-CO-(C₂-C₁₂ alkynyl), -(CH₂)₀₋₄-CO-(C₃-C₇ cycloalkyl), -(CH₂)₀₋₄-CO-aryl, -(CH₂)₀₋₄-CO-heteroaryl, -(CH₂)₀₋₄-CO-heterocyclyl, -(CH₂)₀₋₄-CO-O-R₂₁₅, -(CH₂)₀₋₄-SO₂-NR₂₂₀R₂₂₅, -(CH₂)₀₋₄-SO-(C₁-C₈ alkyl), -(CH₂)₀₋₄-SO₂-(C₁-C₁₂ alkyl), -(CH₂)₀₋₄-SO₂-(C₃-C₇ cycloalkyl),

15 -(CH₂)₀₋₄-N(H or R₂₁₅)-CO-O-R₂₁₅, -(CH₂)₀₋₄-N(H or R₂₁₅)-CO-N(R₂₁₅)₂, -(CH₂)₀₋₄-N(-H or R₂₁₅)-CO-R₂₂₀, -(CH₂)₀₋₄-NR₂₂₀R₂₂₅, -(CH₂)₀₋₄-O-CO-(C₁-C₆ alkyl), -(CH₂)₀₋₄-O-P(O)-(OR₂₄₀)₂, -(CH₂)₀₋₄-O-CO-N(R₂₁₅)₂, -(CH₂)₀₋₄-O-CS-

20 N(R₂₁₅)₂, -(CH₂)₀₋₄-O-(R₂₁₅), -(CH₂)₀₋₄-O-(R₂₁₅)-COOH, -(CH₂)₀₋₄-S-(R₂₁₅), -(CH₂)₀₋₄-O-(C₁-C₆ alkyl) optionally substituted with 1, 2, 3, or 5 -F, C₃-C₇ cycloalkyl, -(CH₂)₀₋₄-N(H or R₂₁₅)-SO₂-R₂₂₀, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl,

25 C₁-C₁₀ alkyl optionally substituted with 1, 2, or 3 independently selected R₂₀₅ groups,

30 C₂-C₁₀ alkenyl and C₂-C₁₀ alkynyl, each of which is optionally substituted with 1 or 2 independently selected R₂₀₅ groups, wherein the aryl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀, or

C₁-C₆ alkyl substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀, and wherein the heterocyclyl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are

5 independently R₂₁₀;

R₂₀₅ at each occurrence is independently selected from C₁-C₆ alkyl, halogen, -OH, -O-phenyl, -SH, -S-C₁-C₆ alkyl, -C≡N, -CF₃, C₁-C₆ alkoxy, NH₂, NH(C₁-C₆ alkyl) or N-(C₁-C₆ alkyl)(C₁-C₆ alkyl);

10 R₂₁₀ at each occurrence is independently selected from halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -NR₂₂₀R₂₂₅, OH, C≡N, -CO-(C₁-C₄ alkyl), -SO₂-NR₂₃₅R₂₄₀, -CO-NR₂₃₅R₂₄₀, -SO₂-(C₁-C₄ alkyl), =O, or C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or C₃-C₇ cycloalkyl, each of which is optionally substituted

15 with 1, 2, or 3 R₂₀₅ groups;

R₂₁₅ at each occurrence is independently selected from C₁-C₆ alkyl, -(CH₂)₀₋₂₋(aryl), C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, and -(CH₂)₀₋₂₋(heteroaryl), -(CH₂)₀₋₂₋(heterocyclyl), wherein

20 the aryl group at each occurrence is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅ or R₂₁₀, and wherein the heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 independently selected R₂₁₀;

25 R₂₂₀ and R₂₂₅ at each occurrence are independently selected from -H, -C₃-C, cycloalkyl, -(C₁-C₂ alkyl)-(C₃-C, cycloalkyl), -(C₁-C₆ alkyl)-O-(C₁-C₃ alkyl), -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₁-C₆ alkyl chain with one double bond and one triple bond, -aryl, -heteroaryl, and -heterocyclyl, and -C₁-C₁₀ alkyl optionally substituted with -OH, -NH₂ or halogen, wherein

30 the aryl, heterocyclyl and heteroaryl groups at each occurrence are optionally substituted with 1, 2, or 3 independently selected R₂₇₀ groups

35

R₂₃₅ and R₂₄₀ at each occurrence are independently H, or C₁-C₆ alkyl;

R₂₄₅ and R₂₅₀ at each occurrence are independently selected from -H, C₁-C₄ alkyl, C₁-C₄ alkylaryl, C₁-C₄ alkylheteroaryl, C₁-C₄ hydroxyalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, and phenyl; or

R₂₄₅ and R₂₅₀ are taken together with the carbon to which they are attached to form a carbocycle of 3, 4, 5, 6, or 7 carbon atoms, where one carbon atom is optionally replaced by a heteroatom selected from -O-, -S-, -SO₂-, and -NR₂₂₀-;

R₂₅₅ and R₂₆₀ at each occurrence are independently selected from

-H, -(CH₂)₁₋₂-S(O)₀₋₂-(C₁-C₆ alkyl), -(C₁-C₄ alkyl)-aryl, -(C₁-C₄ alkyl)-heteroaryl, -(C₁-C₄ alkyl)-heterocyclyl, -aryl, -heteroaryl, -heterocyclyl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-aryl, -(CH₂)₁₋₄-R₂₆₅-(CH₂)₀₋₄-heterocyclyl, and

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl and -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, each of which is optionally substituted with 1, 2, or 3 groups independently selected from

R₂₀₅, -COOH, -COO(C₁-C₄ alkyl), -CO-NH₂, -CO-NH(C₁-C₆ alkyl), -CO-N-(C₁-C₆ alkyl)(C₁-C₆ alkyl), wherein

each aryl or phenyl is optionally substituted with 1, 2, or 3 groups that are independently R₂₀₅, R₂₁₀, or C₁-C₆ alkyl substituted with 1, 2, or 3 groups that

are independently R₂₀₅ or R₂₁₀, and wherein

each heterocyclyl is optionally substituted with 1, 2, 3, or 4 R₂₁₀;

R₂₆₅ at each occurrence is independently -O-, -S- or -N(C₁-C₆ alkyl)-; and

R₂₇₀ at each occurrence is independently R₂₀₅, halogen C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, NR₂₃₅R₂₄₀, -OH, -C≡N, -CO-(C₁-C₄ alkyl), -SO₂-NR₂₃₅R₂₄₀, -CO-NR₂₃₅R₂₄₀, -SO₂-(C₁-C₄ alkyl), =O, or

C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl or -(CH₂)₀₋₄-C₃-C₇ cycloalkyl, each of which is optionally substituted with 1, 2, or 3 R₂₀₅ groups.

13. A compound according to claim 12 that is *N*-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-L-alanyl-*N*¹-isobutyl-L-valinamide.

5 14. The use of a compound or salt according to claim 1 for the manufacture of a medicament.

10 15. The use of a compound or salt according to claim 1 for the manufacture of a medicament for use in the treatment or prevention of Alzheimer's disease, mild cognitive impairment Down's syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, cerebral amyloid angiopathy, other degenerative dementias, dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's 15 disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease.

SEQUENCE LISTING

<110> Warpehoski, Martha A.
Jagodzinska, Barbara

<120> Substituted Amino Carboxamides for the Treatment of Alzheimer's Disease

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<150> 60/345,316
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For two-letter codes and other abbreviations, refer to the "Guid-
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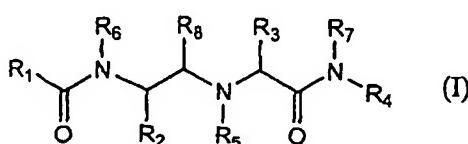
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A3

(54) Title: SUBSTITUTED AMINO CARBOXAMIDES FOR THE TREATMENT OF ALZHEIMER'S DISEASE



(57) Abstract: The present invention relates to compounds of formula (I) useful in treating Alzheimer's disease and other similar diseases. These compounds include inhibitors of the beta-secretase enzyme that are useful in the treatment of Alzheimer's disease and other diseases characterized by deposition of A beta peptide in mammal. The compounds of the invention are useful in pharmaceutical compositions and methods of treatment to reduce A beta peptide formation.

WO 2003/057721 A3

INTERNATIONAL SEARCH REPORT

| |
|---|
| International Application No PCT/US 03/00326 |
|---|

| |
|--|
| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K5/062 C07C237/06 A61K38/05 A61K31/198 A61P25/28 |
|--|

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

| |
|---------------------------|
| IPC 7 C07K C07C A61K A61P |
|---------------------------|

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

| |
|---|
| CHEM ABS Data, WPI Data, BIOSIS, EPO-Internal |
|---|

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 00 77030 A (ELAN PHARM INC) 21 December 2000 (2000-12-21) the whole document ----- | 7-10, 13-15 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

| | |
|---|--|
| Date of the actual completion of the International search | Date of mailing of the International search report |
|---|--|

| 28 October 2003 | 05/11/2003 |

| | |
|--|--------------------|
| Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Authorized officer |
|--|--------------------|

| Groenendijk, M |

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 03/00326**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-6,11,12; 8-10,14,15(partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6,11,12; 8-10,14,15(partially)

The scope of the claims 1-6,12 and the related claims 8-11,14 and 15 is very broad and speculative. A formula consisting virtually of cascading variables which are moreover in at least part of the claims ill-defined (e.g. the use of "aryl" and "heteroaryl") cannot be considered to be a clear and concise definition of patentable subject-matter (Art.6 PCT). Furthermore the available experimental data actually only comprise a very small part of the compounds claimed, which part is moreover not evenly distributed over the whole claimed area and even lacking any data as to the activity of the comprised compounds. Therefore the claims can also not be considered to represent a permissible generalisation which is fairly based on experimental evidence, that is, they are also not adequately supported by the description (Art.6 PCT).

Finally claim 11 lacks any technical feature or even process step which would allow a search.

Therefore it is considered that a lack of clarity, conciseness and support within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, concise and supported, namely the compounds defined in claim 7 and their use and the compound of claim 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/00326

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